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INTERAURICULAR SEPTAL DEFECT

CORRELATION OF THE CLINICAL, RADIOLOGIC, AND ELECTROCARDIOGRAPHIC FINDINGS IN FIFTEEN CASES, WITH SPECIAL REFERENCE GIVEN TO THE ELECTROCARDIOGRAM

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RAPID developments in thoracic surgery over the past few years have placed a new emphasis on the diagnosis of congenital heart disease. The need for establishing the definite location of the defect or defects is apparent. It is through the increased efficiency of diagnosis that the alleviation of certain congenital lesions has in part been realized. Tetralogy of Fallot, patent ductus arteriosus, coarctation of the aorta, and pulmonary stenosis are the lesions that have been amenable to surgery to date.

With this thought in mind, this investigation was initiated in the hope that some pattern, consistent clinically, radiologically, and electrocardiographically, could be found that would help differentiate some of the more confusing congenital heart lesions. Interauricular septal defect was chosen because it is the most common of all single congenital lesions, and it has been difficult in the past to make a definite diagnosis in a young child.

More emphasis has been placed on electrocardiography since it was hoped that with the advent of the precordial and unipolar limb leads, more distinct and characteristic patterns might be revealed in connection with congenital lesions.

It is recognized that additional information could have been obtained by means of cardiac catheterizations and angiocardiography. However, even in the hands of well-trained clinicians, these procedures are not always readily available. It was hoped to point up by these studies the value of information that can be obtained by the more common diagnostic tools.

Most of the remarks in this paper are relative to children unless otherwise stated.

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MATERIAL AND METHOD

Fifteen cases were taken from the pediatric department and analyzed in regard to their clinical, radiographic, and electrocardiographic findings. The data on the cases that will be presented subsequently are an arbitrary selection of the most prominent symptoms and signs found. It should be emphasized that in the cases used in this study, for the most part, diagnoses were made clinically, and in only one instance was there an autopsy to support the clinical diagnosis.

DISCUSSION

The Defect, Its Effect on the Circulatory Dynamics, and the Subsequent Effect on the Heart.—An auricular septal defect is usually relatively large, 2 to 3 cm. in diameter. It should be emphasized that this entity is not synonymous with a patent foramen ovale. There is a definite free communication between the two auricles in interauricular septal defect. Patent foramen ovale merely means that anatomical closure has not occurred. Furthermore, a valve leaflet is usually present over the left side of the foramen, and as long as the left auricular pressure is greater than the right, the foramen is functionally closed.

Because of the free communication between the auricles, auricular septal defects are associated with a shunt of left auricular blood into the right auricle. This left-to-right shunt is the result of the normally greater pressure in the left auricle. The resultant effect would naturally be an increased blood volume in the right heart. It should also be mentioned that in a large defect there is some intermixing of venous and arterial blood at the low pressure part of the cardiac cycle. This is a possible explanation for the production of cyanosis in an occasional patient with this type of defect. It has also been pointed out that the anatomical variation of the great veins emptying into the auricles may influence the production of the cyanosis.[22]

With the resultant alteration of the circulatory dynamics, the right auricle, right ventricle, and pulmonary artery become enlarged.

Clinical Findings.—It has been stated that this defect occurs more often in males than in females, the ratio being as high as 3:1. The sex incidence was practically equal in the cases presented. This observation is substantiated by the series of Roesler[8] who stated that there is definitely no difference in sex incidence.

As Taussig[16] has stated, the characteristic clinical features of the disease are a frail body build (gracile habitus), a left-sided chest deformity (precordial bulge), and no cyanosis or clubbing until the later stages of the disease. Marked cardiac enlargement, which is due to the enlargement of the right auricle and right ventricle, is usually present clinically. A harsh systolic murmur and thrill in the second and third left intercostal spaces are present, and, in addition, it is not uncommon to find some evidence of rheumatic valvular disease. The characteristic clinical symptoms are not always present in infancy, which again makes the diagnosis more difficult in young children. Actually, children with this type of defect may be so-called "blue babies" at birth since normal pressure relationships in the heart may not as yet be established. With the right auricular pressure being greater than the left at birth, a right-to-left shunt is created, which

gives the infant the cyanosis. Only after normal pressure relationships occur does the cyanosis diminish or disappear. The reason that normal pressure relationships occur eventually, in most cases, is that the systemic circulatory pressure becomes greater than that in the right side of the heart.

In reference to the heart sounds in this type of defect, Barber[14] has stated that wide splitting of the second heart sound (attributed to right bundle branch block or to a delay in emptying time of an overfilled right ventricle) is a far more important sign of interauricular septal defect than accentuation of the pulmonary second sound. This observation was not confirmed in our study, although it is recognized that Barber was dealing with older patients. If the etiology is supposedly a complete right bundle branch block, it would not have had time to develop fully in the majority of our patients.

The murmur accompanying an interauricular septal defect is not necessarily characteristic and has been reported[8,17] to be entirely absent in some cases. In the cases analyzed, cardiac murmurs (systolic in character) were present in all. The cause of the murmur and why it should be systolic in time have not been demonstrated. Some authors[8,17] attribute the systolic timing to an enlarged pulmonary artery.

Cardiac enlargement was noted in nine of the fifteen patients, and in four there was definite evidence of heart failure, with the liver being enlarged and palpable in all four. One patient later died; the lesion was confirmed at autopsy. It is granted that the percentage of heart failure in this series is not high, but it occurred often enough that the lesion does not appear to be as innocuous as some would suggest.

In seven cases a definite precordial bulge was present. Underdevelopment occurred in eight cases. In five there was a history of intermittent cyanosis which occurred mainly when the child cried and was not of a continuous nature.

Taussig[16] listed as some of the more common clinical sequelae, which "are of such common occurrence as to be of diagnostic aid," the following: superimposed rheumatic fever infections, pneumonia and other pulmonary infections, and cardiac arrhythmias. She also stated, "No less remarkable than the frequency of the complications is the freedom from subacute bacterial endocarditis."

It is interesting to note that Barber,[14] in a recent article on interauricular septal defect, stated that patients with this defect may lead a normal active life and that its distinction from other forms of congenital heart disease is particularly important because interauricular septal defect requires no protection from bacterial infection. This study does not substantiate this concept since it was found that in the majority of cases frequent, troublesome upper respiratory infections were present, and in five cases there was a definite history of previous episodes of pneumonia. Most authors agree that pulmonary complications should be guarded against.

Radiographic Findings.—Four distinctive radiologic features have previously been outlined[17] as characteristic of this defect. These consisted of enlargement of the right side of the heart, a prominent pulmonary conus, a small aortic knob, and increased hilar shadows (Fig. 1). The increased hilar vascularity gives

TABLE I. CLINICAL FINDINGS

	NO. CASES
Colds and upper respiratory infections	8
Previous history of pneumonia	5
Underdevelopment	8
Cyanosis	5
Heart murmur (systolic)	15
Heart enlargement	9
Precordial bulge	7
Cardiac failure	4

rise to the so-called "hilar dance" (vascular pulsations) seen by fluoroscopy. While the radiographic findings are important diagnostic signs, they are not always consistent nor do they always substantiate the clinical and electrocardiographic findings.

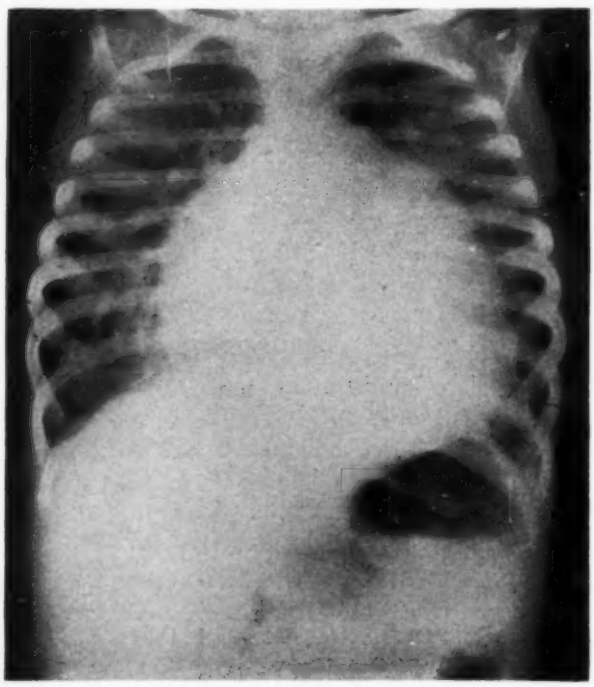

Fig. 1 (Case 7).—This roentgenogram shows the typical configurations seen in interauricular septal defects: (1) cardiac enlargement, (2) prominent pulmonary outflow tract, and (3) increased bronchovascular markings.

Ten of the patients in this study showed prominent pulmonary arteries by roentgenogram. A definite hilar dance was observed by fluoroscopy in eight instances. This finding has proved particularly useful in differentiating hilar shadows due to increased vascularity from hilar shadows of nonvascular origin. There was fairly definite evidence of right heart enlargement in twelve cases. Two of these (Cases 3 and 4) showed right heart enlargement only on the right anterior oblique views which points up the necessity for oblique views in de-

TABLE II. RADIOGRAPHIC FINDINGS

	NO. CASES
Right heart enlargement	12
Combined right and left heart enlargement	2
No heart enlargement	3
Enlargement of the pulmonary arteries	10
Hilar dance	8

termining heart enlargement radiographically. It should also be noted that three of the patients showed no evidence of cardiac enlargement by roentgenogram and yet showed definite evidence of right ventricular hypertrophy by the electrocardiogram.

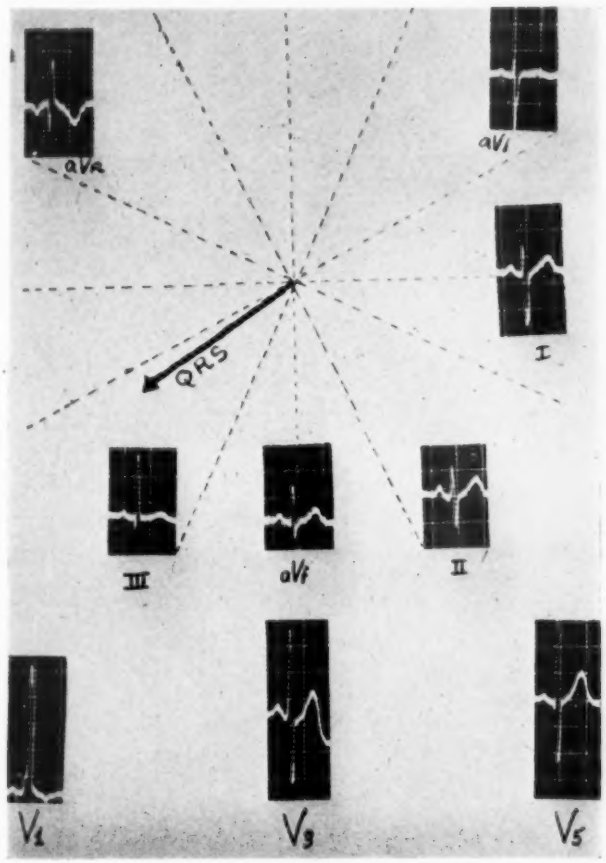

Fig. 2 (Case 5).—An electrocardiogram illustrating right axis deviation of plus 140 degrees and right ventricular hypertrophy.

Electrocardiographic Findings.—The changes in the electrocardiogram associated with auricular septal defects may be divided into three categories: those due to auricular hypertrophy, those due to right ventricular hypertrophy, and those due to arrhythmias.

Auricular enlargement is manifested by an increased amplitude and occasional notching of the P wave. The enlarged auricle produces a greater electromotive force during its depolarization, resulting in this finding. Evidence of auricular enlargement electrocardiographically is not a constant finding, however, and was demonstrated in only two cases of this series. This is consistent with other observers,[10,17,20,21] who stated that abnormal P waves are definitely the exception, and their absence should in no way deter one in making the diagnosis if other compatible diagnostic criteria are present. It should be noted that P waves in children are normally larger than in adults. Ashman[4] placed the upper limit of normal for the height of the P wave in Lead I at 1.5 mm. and in Lead II at 2.5 mm.

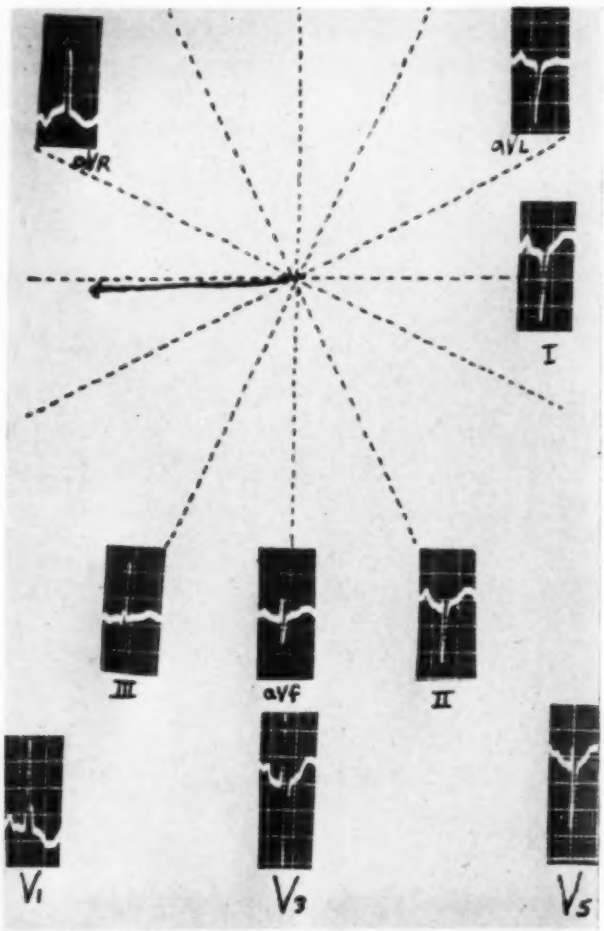

Fig. 3 (Case 13).—An electrocardiogram showing right axis deviation of plus 180 degrees resulting in a tall R wave in aV_R. There is a delay in the intrinsicoid deflection to 0.04 second, and the P-R interval is prolonged for the age and cardiac rate to 0.16 second. The record is interpreted as right axis deviation, right ventricular hypertrophy, and first-degree heart block.

Right ventricular hypertrophy, seen electrocardiographically in all fifteen patients in this series, is manifested by a delay in the intrinsicoid deflection over

the right ventricle and the appearance of right axis deviation (Fig. 2). The delay in the intrinsicoid deflection is usually best seen in the V_1 position or, in extreme enlargement of the right side of the heart, in leads taken to the right of the sternum. The normal intrinsicoid deflection of the right ventricle does not exceed 0.03 second. With right ventricular enlargement, the heart also rotates on its base in a clockwise fashion, so that the left ventricle becomes posterior in position and rests largely on the diaphragm. This rotation results in a change in the transition zone from right to left ventricular patterns (seen in the precordial leads) so that it occurs as far to the left as position V_5 or V_6. If the enlargement of the right ventricle is sufficient to rotate the force of depolarization toward the right arm, a tall R wave is seen in aV_R (Fig. 3).

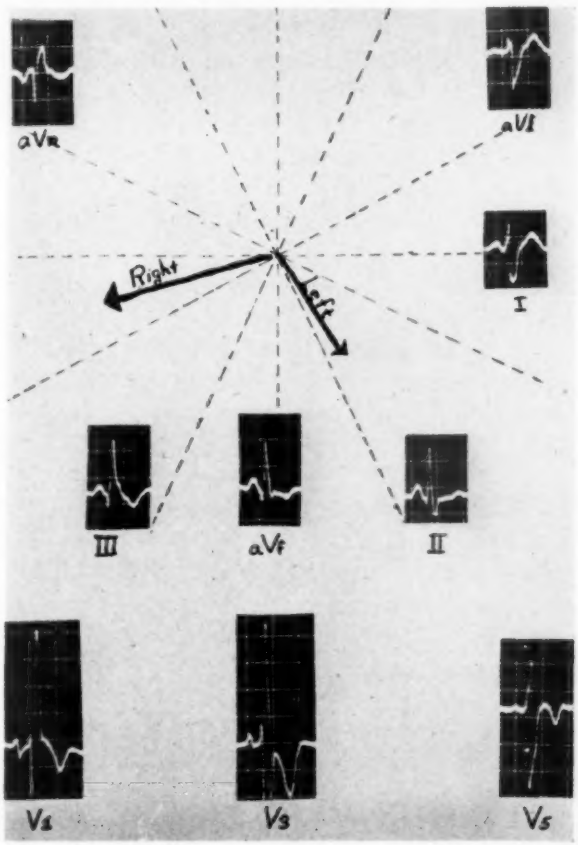

Fig. 4 (Case 10). An electrocardiogram showing right bundle branch block as evidenced by prolongation of the QRS complex to 0.12 second and a delay in the intrinsicoid deflection to 0.05 second in V_1. The right vector indicates the direction of depolarization of the right ventricle, and the left vector indicates the direction of depolarization of the left ventricle.

It is interesting to note that five of the patients showed no evidence of right axis deviation by the standard limb leads, while the unipolar and precordial leads, as well as the clinical and radiographic findings, substantiated the finding of right ventricular enlargement. Roesler,[8] in his extensive series, also found that the interesting finding from the electrocardiographic point of view was the

presence, as a rule, of only a moderate degree of right axis deviation when the standard limb leads were used, although radiographically, clinically, and at autopsy there were enormous dilatation and enlargement of the right side of the heart.

In evaluating the findings of right axis deviation and right ventricular hypertrophy, it should be remembered that a normal infant may present these findings, since the right ventricle is larger than the left ventricle at birth and therefore dominates the forces of depolarization. Four months, and in some cases as long as two years, are required for the left ventricle to become larger than the right ventricle.

Right bundle branch block is not an uncommon finding in auricular septal defects and is manifested on the electrocardiogram by a delay in the intrinsicoid deflection over the right ventricle and a prolongation of the duration of the QRS complex. It should be noted that the normal values for the duration of the QRS complex in children are different than those for adults, the upper limit of normal ranging from 0.08 to 0.09 second. Complete right bundle branch block was noted in one patient in this study (Fig. 4). Disturbance in conduction between the auricles and ventricles may also be seen; it is shown electrocardiographically by a prolongation of the P-R interval. The P-R interval is normally shorter in children than in adults. Ashman[4] has said that until the fifth year of age, the P-R interval is about 0.11 to 0.12 second, from 6 to 9 years 0.13 second, from 10 to 12 years 0.135 second, and from 13 to 14 years about 0.14 second. The P-R interval should not exceed the average figure for that age group by more than 0.02 second when the heart rate is rapid or by more than 0.04 second when the heart rate is slow. Any prolongation in the P-R interval above these normal limits is considered as evidence of an atrioventricular conduction defect or first-degree heart block. Prolonged P-R interval, according to the criteria of Ashman, occurred in ten of the fifteen patients in this series. Barber[14] showed that it tended to range around the upper limits of normal or above in most of his patients.

Auricular septal defects are commonly associated with paroxysms of auricular tachycardia and auricular fibrillation, this defect being the most common cause of auricular fibrillation in congenital heart disease. Taussig[16] attributed this to the abnormal degree of auricular enlargement.

TABLE III. ELECTROCARDIOGRAPHIC FINDINGS

	NO. CASES
Right axis deviation	10
Increased amplitude of the P waves	2
Prolonged P-R interval	10
Right bundle branch block	1
Evidence of right ventricular hypertrophy	15

In summary, the electrocardiographic features that may be encountered in auricular septal defects include enlarged P waves associated with auricular enlargement, right ventricular hypertrophy and right axis deviation associated

with right ventricular enlargement, and conduction defects in the form of right bundle branch block, auriculoventricular block, auricular tachycardia, and auricular fibrillation.

Differential Diagnosis.—The conditions from which this malformation must be differentiated include other common congenital heart defects of the acyanotic type. Some of the more important differential points are given as follows:

1. *Patent ductus arteriosus*: This condition presents a characteristic heart murmur in most cases and is one of the few diseases in which the heart murmur alone will almost establish the diagnosis. It is described as a "machinery" murmur, continuous throughout the diastolic and systolic components of the heart cycle, being of greatest intensity during the systolic phase. In early infancy, however, the characteristic murmur may not be present. This is due to the fact that the pulmonary artery pressure may be equal to the pressure in the aorta, producing only the systolic component of the murmur. After normal pressure relationships occur (aortic pressure greater than pulmonary artery pressure), the continuous murmur will be produced.

Ventricular enlargement, when it occurs, involves the left ventricle and may be demonstrated by roentgenographic and electrocardiographic studies.

2. *Isolated pulmonic stenosis*: This lesion is sometimes difficult to distinguish, since clinically and electrocardiographically it may resemble the picture of interauricular septal defect. However, the radiographic findings are usually characteristic, in that the pulmonary conus is not always prominent and the lung fields are relatively avascular.

3. *Interventricular septal defect*: Clinically, this condition will usually show normal growth and development. A harsh systolic murmur and thrill are present over the precordium, the murmur being described as "exactly systolic" in character. Most often, the electrocardiogram will show no unusual characteristics. The radiographic findings are usually not remarkable although in a rare instance the defect may be high enough in the ventricular septum to cause enlargement of the auricles and pulmonary artery; this will be shown radiographically. Ventricular enlargement, when it occurs, commonly affects both ventricles.

SUMMARY

The clinical, radiographic, and electrocardiographic findings in fifteen cases of interauricular septal defect have been presented.

No specific pattern or patterns were seen that could be considered absolutely diagnostic for this defect. However, it would seem that accurate diagnoses can be made with proper correlation of the clinical, radiographic, and electrocardiographic findings, even though a physician does not have the highly specialized diagnostic procedures at his disposal, such as angiocardiography or cardiac catheterization.

Clinically, the lesion does not appear as innocuous in children as some suggest. Heart failure can and does occur. Upper respiratory infections, which occur frequently, should be guarded against because of their complicating sequelae.

Electrocardiographically, it was seen that right ventricular hypertrophy can only be shown consistently by the use of the precordial and unipolar limb leads. No specific electrocardiographic pattern was seen to be absolutely diagnostic, but the electrocardiographic variations that may be seen in an auricular septal defect have been discussed.

CASE REPORTS

CASE 1.—J. R., a 28-month-old white girl, was discovered to have a cardiac murmur at the age of 6 days. She has otherwise been asymptomatic.

Physical examination revealed a palpable systolic thrill at approximately the third left intercostal space. There was cardiac dullness to the left mid-clavicular line in the fourth intercostal space. A harsh, moderately prolonged systolic murmur was heard over the precordium. It was maximal at the third left intercostal space and was transmitted to the apex. No diastolic component was heard.

Radiographically, there was a moderate cardiac enlargement chiefly of the right ventricle, as visualized in the anteroposterior view. The pulmonary arteries were prominent. The electrocardiogram revealed right ventricular hypertrophy.

CASE 2.—D. S., a 2-year-old white boy, was first noted to have a heart murmur at 3 months of age. The patient had experienced frequent upper respiratory infections and had a slow weight gain. Transient cyanosis had been noted occasionally.

Physical examination revealed a small, underdeveloped child with no visible cyanosis but an obvious increased respiratory rate. There was slight bulging of the precordium. A loud systolic murmur was heard to the left of the sternum at the second to fourth intercostal space. There was cardiac enlargement to percussion. The pulmonic second sound was markedly accentuated.

Other than the prominence of the pulmonary conus, the heart and lungs were considered normal radiographically. An electrocardiogram showed right axis deviation and evidence of right ventricular hypertrophy by the unipolar limb and precordial leads.

CASE 3.—J. C., an 8-year-old white boy, was first noted to have a heart murmur at 6 months of age and has had exertional dyspnea since that time. His development has apparently been normal. Past history included an episode of pneumonia and otitis media and frequent upper respiratory infections.

Physical examination revealed a well-developed white boy. There was a palpable systolic thrill at the suprasternal notch. A harsh systolic murmur was heard maximal over the pulmonic area with wide transmission over the entire precordium. No diastolic component was heard.

Fluoroscopic examination revealed a heart within normal limits in size, although there was prominence of the right ventricle and right auricle, especially in the oblique views. The pulmonary arteries were prominent but not hyperactive. The peripheral lung vascular markings were normal. The electrocardiogram showed evidence of right ventricular hypertrophy and prolongation of the P-R interval.

CASE 4.—M. F. a 3-year-old white girl, was seen with a history of a heart murmur since birth. The mother had noted cyanosis upon crying since birth and had noticed exertional dyspnea since the child began walking. The child had experienced frequent upper respiratory infections and had had bilateral draining otitis media on two occasions.

Physical examination showed a well-developed white girl. Examination of the chest showed a moderate precordial bulge. There was no enlargement of the heart to percussion. A systolic thrill was present at the base of the heart. There was a loud, prolonged, and harsh systolic murmur heard over the precordium, maximal at the third left intercostal space.

Fluoroscopy revealed the heart to be within normal limits in size, but in the right anterior oblique view there appeared to be definite enlargement of the right ventricle. The lung vascular markings appeared to be within normal limits. Electrocardiographically, the tracing showed evidence of right ventricular hypertrophy.

CASE 5.—C. H., a 21-month-old white girl, presented a history of recurring cyanosis beginning at birth and continuing until the age of 6 weeks. At that time she was given x-ray therapy, sup-

posedly to the thymus gland, with complete cessation of such episodes. The child had since been quite active, presenting at no time any symptoms of cardiac distress. Past history revealed one episode of upper respiratory infection.

Physical examination revealed a well-developed girl. There was a palpable systolic thrill in the suprasternal notch and over the carotid vessels. The chest showed no thoracic deformity. The heart revealed a palpable systolic thrill over the pulmonic area. There was no enlargement to percussion. A harsh systolic murmur, maximal over the pulmonic area, was heard with excellent transmission down the left sternal border to the apex. There was also transmission throughout the thorax and especially over the upper back. No diastolic component was heard.

Roentgenograms and fluoroscopy revealed the heart to be of normal size and configuration. The barium swallow was normal. The lung vascular markings were normal. An x-ray film of the heart, however, suggested a prominence of the pulmonary conus and pulmonary arteries. An electrocardiogram was compatible with right ventricular hypertrophy and showed a prolongation of the P-R interval.

CASE 6.—S. S., an 11-year-old white boy, was admitted to the hospital with a diagnosis of congenital heart disease and mental retardation. There was no known cyanosis. His activity had been limited only in that he "tires more readily than the other children."

On physical examination the heart was not enlarged to percussion. There was a systolic thrill at the fourth intercostal space approximately 3 cm. to the left of the sternum. A systolic murmur was heard over the area and transmitted to the base of the heart. Moderate exertional dyspnea was noted.

X-ray studies demonstrated a large right side of the heart with apparently normal pulmonary arteries. The electrocardiogram showed right ventricular enlargement and auricular hypertrophy. The P-R interval was prolonged.

CASE 7.—S. J., a 10-month-old girl, was known to have had a heart murmur and cardiac enlargement since birth. She had frequent upper respiratory infections and had had pneumonia three months prior to admission. Ten days prior to admission she began to have puffiness about the eyes, and four days prior to admission swelling of the extremities was noted.

Physical examination revealed a child in acute distress with generalized swelling of the extremities. The heart was enlarged to percussion, and there was a harsh precordial systolic murmur with a diastolic rumble at the apex. There was a palpable systolic thrill over the precordium, and the liver was palpated 3 fingerbreadths below the right costal margin.

Roentgenograms showed the cardiac silhouette to be above limits of normal in size. There was a marked increase in the size of the right side of the heart. There was prominence in the pulmonary outflow tract, and the bronchovascular markings were markedly increased. The electrocardiogram revealed auricular hypertrophy and right ventricular hypertrophy.

CASE 8.—S. C., a 7-month-old child, was said to have been cyanotic at birth, but the cyanosis disappeared shortly thereafter. A heart murmur was also noted at birth. The patient had pneumonia at the age of 5 months and failed to gain weight properly from that time.

Physical examination revealed a poorly nourished and somewhat pale child. The heart was not enlarged to percussion. There was a loud harsh systolic murmur heard best in the third and fourth intercostal spaces to the left of the sternum. The liver was palpated one fingerbreadth below the right costal margin.

X-ray findings, together with the increased bronchovascular markings, were suggestive of enlargement of the right auricle. The electrocardiogram showed evidence of right ventricular hypertrophy and prolongation of the P-R interval.

CASE 9.—W. F., a 4-month-old white boy, was known to have had a heart murmur since birth. He had frequent colds and had pneumonia a week prior to admission. The child had been slow in development.

Physical examination revealed a poorly developed boy with rapid respirations. A slight anterior bulge of the left side of the chest was noted. There was a systolic murmur with an accentuated second sound heard over the precordium. The liver was palpated 2 fingerbreadths below the right costal margin.

Roentgenograms showed enlargement of the right ventricle and prominent bronchovascular markings. The electrocardiogram was compatible with right ventricular enlargement and showed prolongation of the P-R interval.

CASE 10.—J. H., a 13-year-old child, came to the hospital with a history of having had congenital heart disease since birth. Four months prior to admission the patient developed a febrile illness with polyarthritis, elevated sedimentation rate, and a diagnosis of rheumatic fever. About three weeks prior to admission, the patient began having dyspnea. Orthopnea, dyspnea, cyanosis, swelling of the abdomen, and nausea and vomiting were all present four days prior to admission.

Physical examination revealed an acutely ill child with respiratory distress. There was a definite bulging of the left side of the chest anteriorly. The heart was enlarged to percussion, the point of maximal impulse extending to the sixth intercostal space in the left mid-clavicular line. The right heart border was approximately 2 to 3 cm. to the right of the mid-sternal line. There was a loud systolic murmur heard over the apical region with a diastolic rumble. The systolic murmur was also heard over the base of the heart along the left sternal border. The liver was enlarged 3 to 4 cm. below the right costal margin.

Radiographically, the heart was above the normal limits in size. The enlargement was primarily of the right ventricle. There was displacement of the barium-filled esophagus posteriorly. The hilar areas of the lungs were congested. The electrocardiogram revealed a right bundle branch block and prolongation of the P-R interval.

CASE 11.—K. S., a 2-year-old white girl was known to have had a heart murmur since birth. She had one episode of pneumonia five months prior to admission.

Physical examination revealed a precordial bulge. The respiratory rate was markedly increased. The heart was enlarged to percussion, the apex being at the anterior axillary line at the level of the sixth intercostal space. There was a systolic thrill, and a systolic murmur was best heard in the third left intercostal space and present over the entire precordium.

Roentgenograms showed the cardiac silhouette to be markedly enlarged with the enlargement involving chiefly the right ventricle and both auricles. Moderate prominence of the pulmonary conus was noted. The electrocardiogram revealed right ventricular hypertrophy and prolongation of the P-R interval.

CASE 12.—G. C., a 5-month-old white boy, was known to have had rapid respiration since birth. The child was seen by a family physician who diagnosed an enlargement of the thymus, and the child was given four x-ray treatments. At the age of 4 months the child was hospitalized eight days with a diagnosis of pneumonia.

Physical examination revealed a child with rapid respiration and marked retraction of the costal margins. There was a precordial bulge present. The heart was enlarged to percussion, but no thrill was palpated. A systolic murmur was best heard at the third left intercostal space and was transmitted through the chest. The liver was palpated one fingerbreadth below the right costal margin.

Radiographically, the heart was enlarged, involving primarily the right ventricle. The electrocardiogram revealed right ventricular hypertrophy.

CASE 13.—R. B., a 2-year-old white boy, had had a cardiac murmur since birth. He had frequent upper respiratory infections, but the history was otherwise unremarkable.

Examination showed a moderately protuberant sternum. There was a palpable systolic thrill over the precordium. A harsh prolonged systolic murmur was heard, maximal at the third left intercostal space, well transmitted throughout the chest. There was a localized apical diastolic rumble.

Fluoroscopy and roentgenograms of the heart revealed some degree of right ventricular hypertrophy. The lung vascular markings were prominent. The electrocardiogram was compatible with right ventricular hypertrophy. It also showed first-degree heart block.

CASE 14.—A. H., a 21-month-old white girl, was admitted to the hospital with a heart murmur. The patient had been bothered frequently with upper respiratory infections. Her mother also stated that the child tired easily when she played.

Physical examination was essentially negative except for a harsh systolic murmur present over the entire precordium.

Fluoroscopic and radiographic examination revealed a heart whose contour was essentially normal. Lateral views gave the impression of hypertrophy of the right side of the heart. The electrocardiogram was indicative of right ventricular hypertrophy and showed prolongation of the P-R interval.

CASE 15.—J. F., a 9-day-old white boy, who had rapid respirations was noted to have a heart murmur.

Physical examination showed a cyanotic child who appeared to be in shock. There was a loud systolic murmur over the entire precordium. The liver was palpated 3 fingerbreadths from the right costal margin.

Fluoroscopic examination of the chest showed inadequate aeration of the lungs but a heart contour and size that was not thought to be suggestive of significant disease. The electrocardiogram revealed right ventricular hypertrophy.

The child continued to do poorly and in spite of intensive therapy died in cardiac failure. The autopsy revealed a large defect in the interauricular septum.

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THE EFFECTS OF POSTURE ON A-V CONDUCTION

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CHANGES which appear in the heart rate and in the blood pressure when normal persons assume the upright position have often been carefully studied and are well known. Alterations in the circulatory apparatus in cardiac patients who assume different postures are diversified and, for a great part, are not thoroughly explained. It is not known, for example, why murmurs, particularly those associated with rheumatic mitral stenosis, often disappear with the patient in the erect posture, while other murmurs may become audible or may be more easily heard with the patient standing. It is also not explained why gallop rhythm may be very pronounced when the patient is recumbent but is often absent when he stands.

Since Einthoven's pioneer work,[3] it has also been realized that in the healthy person changes in the electrocardiogram appear when a new posture is assumed. Differences in the form of the QRS complexes as well as modifications of the duration of the Q-T interval may be noted. Marked alteration of the RS-T segments and the T waves and variations of rhythm are also found. Extrasystoles[14] or asystole[2] may appear only when the patient stands, and heart block may appear or become aggravated when the patient is erect.[4,9]

Of particular interest, and the subject of the present study, is the diminution or the disappearance of an A-V block when the patient assumes the sitting or standing position.[16,19] This phenomenon has been studied in recent years by several authors. Alexander and Bauerlein[1] as well as Holmes and Weill[6] presented cases showing a lower degree of heart block and a marked shortening of the P-R interval when the patient changed from the recumbent to the upright position. In some instances the authors observed these changes without concomitant variations of rate. Poel[15] reported a 15-year-old boy with a prolonged P-R interval in the recumbent position and a marked shortening of the A-V conduction time when he was standing. Manning and Stewart[11] reported four cases of A-V block among a total of twenty in which the P-R interval was definitely reduced on change from the recumbent to the upright position. Stein also reported two cases of partial A-V block (the one patient whom the author diagnosed as having complete block also exhibited partial block) with a diminished degree of block on standing.

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In each of these reports only one to four patients having postural changes in the P-R interval were investigated. We therefore decided to study these positional alterations of the A-V conduction time on a larger number of patients in order to be able to estimate their incidence and to ascertain whether any conclusions could be drawn.

Most previous authors reported the immediate appearance of the shortening of the P-R interval on standing and the immediate return to its former length on reassumption of the supine position. Since these changes were attributed to a change of nerve tonus (usually of vagus tonus), we expected that continuous variations of the length of the P-R interval should be found. An immediate stabilization of nerve tonus appeared improbable. Therefore, not only did we study the electrocardiogram immediately after the changes of position, but we took continuous tracings repeatedly for fifteen to thirty minutes during the standing time and for ten minutes after the patient reassumed the horizontal position.

METHOD

The investigations were done on a consecutive series of thirty-one patients who had an A-V conduction disturbance and who were able to stand. Lead II was taken in most cases because this offered the possibility of measuring the P-R intervals more exactly. In some patients 3 mg. of atropine sulfate were injected intramuscularly, and in some other patients the effect of physical exertion on A-V conduction was studied. No accident nor any alarming untoward reactions were observed.

RESULTS

The data obtained from our patients are compiled in Table I. In the second column are listed the P-R time in hundredths of a second and the rate per minute. In the third and fourth columns the first figure is time spent in the erect or recumbent position, respectively; the other figures are the P-R times and the rates, respectively. Thus, 4/22/108 in the third column indicates that after four minutes of standing the P-R interval was 0.22 second, and the rate was 108 beats per minute. The abbreviation Imm. indicates immediately after standing or lying, although in many cases continuous records were not taken during the change of position so that there was a lapse of time, usually from about thirty seconds to one minute, between recordings.

No change was found in one case of complete A-V block. Of the thirty cases of partial A-V block investigated, twenty-six revealed a shortening of the P-R interval when the patients changed from the recumbent to the upright position. As the table reveals, in many cases the shortening was considerable. Only in one patient (Case 8) did it amount to only 0.01 second. It is noteworthy that in three of the four patients with no shortening of the prolonged P-R intervals on standing, a bundle branch block existed. One patient with bundle branch block showed a shortening of the A-V conduction by 0.03 second when the patient assumed the standing position.

TABLE I.

CASE	CONTROL (P-R/RATE PER MINUTE)	STANDING TIME/P-R/RATE PER MINUTE	RECUMBENT TIME/P-R/RATE PER MINUTE	REMARKS
1	26/68	1mm/24/74 5/16/90	1mm/20/66 2/26/62	32-year-old man with primary atypical pneumonia; no digitalis
2	20/76	1mm/16/98 5/14/100 10/16/84	1mm/20/74	30-year-old woman with active rheumatic heart disease; no digitalis given
3	21/72	1mm/15/104 5/15/104 10/14/104	1mm/14/68 1/19/58 2/22/60	15-year-old girl with primary atypical pneumonia; no digitalis
4	20/62	1mm/18/70 3/18/78 10/18/78	1mm/19/72 ½/20/64 2/20/62	29-year-old man with patent ductus arteriosus; no digitalis
5	22/102	1mm/20-21/106 1/20/104 7/20/106	1mm/22/104 1/22/102 5/22/102	49-year-old woman; no digitalis; no demonstrable organic illness
6	28/86	1mm/18/86 ½/24/96 1/18/96 5/22/104 15/20/96	1mm/26/70	13-year-old boy with active rheumatic fever
7	26/100	1mm/24/108 2/26/100 6/26/100	1mm/26/100	75-year-old woman; on digitalis; atropine 5 mg. I.M. given with patient recumbent shortened P-R from 26 to 24 and rate increased to 116 with gradual return to normal; thus, with atropine: control 26/70, 10/24/116, 15/24/116, 30/26/105
8	25/83	1mm/24/88 2/24/87 6/24/86 10/24/86	1mm/24/83 3/25/81	56-year-old man; on digitalis; arteriosclerotic heart disease
9	24/78	1mm/20/102 4/22/108 6/22/108 10/20/110	1mm/22/80 1/23/74 3/24/74	23-year-old woman with pneumonitis; no digitalis; after exercise (bending the knees 25 times) and in recumbent position P-R/rate = 18/98
10	28/64	1mm/24/82 10/24/74 30/24/70	1mm/28/62	60-year-old woman; no digitalis; after 30 minutes of standing, no further P-R change from that obtained immediately
11	24/76	1/24/79 5/24/78 10/24/78	Not done	No change; right bundle branch block present
12	28/70	1/17/86 2/16/98	Not done	No further data available

TABLE I.—CONT'D

CASE	CONTROL (P-R/RATE PER MINUTE)	STANDING TIME/P-R/RATE PER MINUTE	RECUMBENT TIME/P-R/RATE PER MINUTE	REMARKS
13	21/73	1/17/108 2/17/96	Temporary A-V rhythm	18-year-old girl with active rheumatic fever; no digitalis
14	28/84	1/25/100 5/25/98 10/25/100	Not done	66-year-old woman with hypertensive arteriosclerotic heart disease; on digitalis; left bundle branch block
15	28/60	1/28/55 5/28/56 10/28/56	Not done	76-year-old man with hypertensive arteriosclerotic heart disease and pulmonary fibrosis; on digitalis; left bundle branch block present
16	20/68	1/16/88 2/20/66	Imm/20/70	12-year-old boy with active rheumatic fever; no digitalis; P-R here seemed to vary with rate even regardless of position
17	33/74 Repeated 25/98	1/29/79 5/29/80 1/23/101 5/23/102	Imm/30/78 Imm/25/98	37-year-old man with inactive rheumatic fever; no digitalis
18	32/56	1/30/68 2/30/66	Imm/31/60	After standing for 5 minutes, the patient developed A-V rhythm
19	28/104	2/20/138	2/26/96	
20	Complete heart block	No change	No change	62-year-old man with generalized arteriosclerosis; on digitalis; no change after standing 10 minutes
21	20/80	1/16/86 5/16/86 10/16/86	Not done	88-year-old man with hypertensive arteriosclerotic heart disease and emphysema; no digitalis
22	29/60	1/29/62 5/29/60	Not done	65-year-old man with arteriosclerotic heart disease; on digitalis; right bundle branch block present
23	20-24/72	1/19/80 2/19/86 5/16/92	24-25/68	P-R interval varied in association with the sinus arrhythmia with the patient in recumbent position
24	24/56	1/20/66 3/20/70 10/18/60	Not done	
25	26/56	1/21/72 2/24/68 5/22/68	Imm/26/56	72-year-old man with hypertensive arteriosclerotic heart disease and diabetes; old cerebral vascular accident; not on digitalis
26	23/56	1/23/60 2/23/62 5/23/62	Imm/23/56	85-year-old man with arteriosclerotic heart disease; not on digitalis; no change

TABLE I.—CONT'D

CASE	CONTROL (P-R/RATE PER MINUTE)	STANDING TIME/P-R/RATE PER MINUTE	RECUMBENT TIME/P-R/RATE PER MINUTE	REMARKS
27	32/72	Imm/29/84 2/30/81 4/28/80 8/28/82	Imm/28/80 with gradual increase to 32/76	70-year-old man; not on digitalis; exercise increased rate and decreased P-R interval; breath holding also increased rate and decreased P-R interval; in other cases, breath holding slowed rate
28	24/69	Imm/20/78	Imm/22/74 2/24/62	54-year-old man with arteriosclerotic heart disease; on digitalis; flexing thighs on hip while in recumbent position increased the rate (64-78) without changing the P-R interval
29	Wenckebach periods	Change to sinus rhythm with P-R of 0.28	Wenckebach periods	58-year-old woman with coronary sclerosis
30	21/62	Imm/19/74	Imm/19/76 Gradual P-R increase to 21/60	54-year-old woman with arteriosclerotic heart disease; no digitalis; P-R interval short (18-20) for complex following premature ventricular contraction
31	22/78	Imm/20/90 1/18/94	Imm/18/86 with gradual return to 22/70	47-year-old man with acute alcoholism; flexing thighs on hips had no demonstrable effect on the P-R interval

It is not necessary to record details of our results as the information is presented in the table. Only the more remarkable findings will be discussed and illustrated.

In one patient (Case 10) the administration of 3 mg. of atropine sulfate intramuscularly shortened the P-R interval from 0.28 to 0.26 second with a marked increase of the rate (from 58 to 80 per minute). When the patient stood, however, the P-R interval decreased to 0.24 second while the heart rate increased from 64 to 70.

Fig. 1 shows tracings obtained from a boy, 13 years old, with active rheumatic fever (Case 6). Fig. 1,*A* shows Lead II taken in the recumbent position when the rate was 86 beats per minute, and the A-V conduction time was 0.28 second. The T waves were normally positive. When he stood (Fig. 1,*B*), without any change of rate, the P-R interval was reduced to 0.18 and gradually rose again to 0.24 second. The T wave became flat. Thirty seconds later (Fig. 1,*C*) the rate was 96, and the P-R interval measured 0.24 second. After he had been standing for one minute, the heart rate was 96, the P-R interval was 0.18 second, and the T wave was slightly higher (Fig. 1,*D*). After he had been standing for five minutes, the rate had risen to 104 (Fig. 1,*E*), the P-R interval had become 0.22 second, and the T wave was again smaller. Finally, when he resumed the supine posture, we registered a prolongation of the P-R interval

to 0.26 second with a rate of 70 (Fig. 1,*F*). A marked respiratory arrhythmia existed, and it is interesting that, following a disastole of 1.02 second, the P-R interval had the same length as one following a diastole lasting 0.80 second. The T wave became normal again.

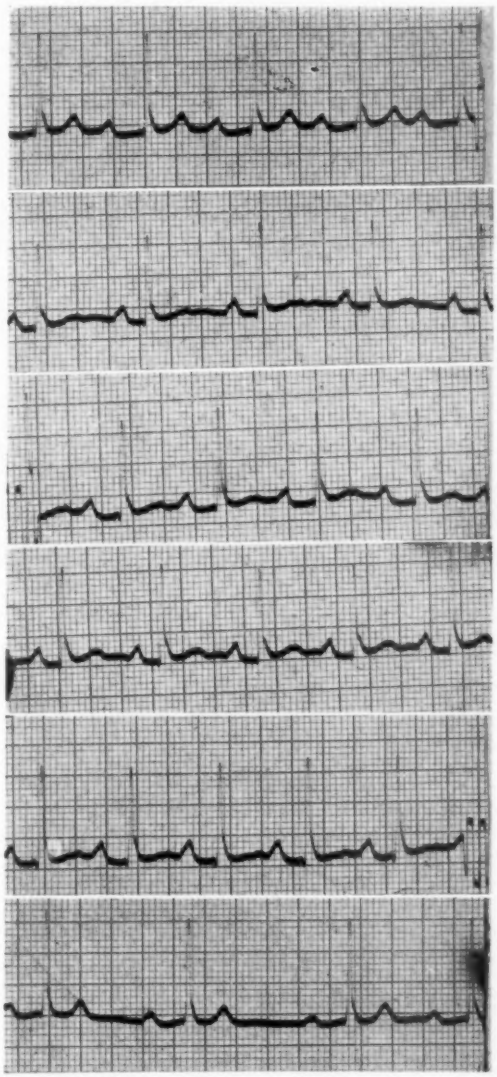

Fig. 1.—*A* shows the prolonged P-R interval when the patient is in the supine posture. *B* to *E* show the variations which appeared during prolonged standing. *F* shows the electrocardiogram obtained immediately when the patient resumed the supine posture (Lead II).

This case distinctly demonstrates the shortening of the P-R interval when the patient stood before an increase of rate occurred and the variations in the duration of the P-R interval during the first few minutes after a change of position. When the patient lay down, the P-R interval was again prolonged, although not immediately, to its former value. The duration of the A-V conduction time is to some degree independent of the heart rate.

Fig. 2 shows tracings obtained from a 15-year-old girl with atypical pneumonia (Case 3). At rest and in the supine position the rate was 72 per minute, and the P-R interval was only 0.21 second (Fig. 2,*A*). When she stood, the rate increased to 104, and the P-R interval shortened to 0.15 second (Fig. 2,*B*). The T wave became much lower. After ten minutes of standing the rate was the same, but the P-R interval had fallen to 0.14 second. When she lay down, the T wave instantly became higher, the rate slowed to 68 (Fig. 2,*C*), and the P-R interval gradually increased from 0.14 to 0.19 second. After she had been two minutes in the supine position the T wave became higher (Fig. 2,*D*), and, with a rate of 60, the P-R interval measured 0.22 second.

Here again one finds that the changes did not appear to their full extent immediately on change of posture and that variations were observed. On continuous standing, a progressive shortening and, on continuous lying, a progressive lengthening of the P-R interval were observed.

Fig. 3 was registered from the same patient as Fig. 2, and it illustrates the effect of deep breathing on the electrocardiogram. The beginning of the tracing shows the effect of inspiration with breath holding. The rate accelerated, and the P-R interval was reduced from 0.21 to 0.18 second. In the center of the tracing, with the patient maintaining the inspiratory position, the P-R interval was 0.21 second in spite of the slow rate. With the beginning of expiration, toward the end of the tracing, the P-R interval was reduced to 0.16 second although the rate was still slow. This experiment was repeated with the same result. The changes of the P-R interval were independent of the rate.

In one patient in whom Wenckebach periods appeared during active rheumatic fever (Case 29 of Table I), the phenomenon disappeared after 18 to 20 beats elapsed with the patient standing and reappeared after the same number of beats when the patient was again supine.

Fig. 4 was obtained from a 19-year-old man with active rheumatic fever and shows a marked sinus arrhythmia of unknown cause. The P-R interval was prolonged and its duration varied depending on the duration of the preceding diastole. Standing did not influence the arrhythmia, and the A-V conduction time and the tracing maintained the same pattern. Following the intramuscular injection of 3 mg. of atropine sulfate, the auricular rate increased to 110, and a complete A-V block appeared.

In addition to changes in the P-R interval, modifications of the T waves and of the RS-T segments were often observed. These alterations were not simultaneous. Often the T waves changed immediately with the assumption of the erect posture and also reverted to normal immediately with the patient in the recumbent position, while the alterations of the A-V conduction time appeared slightly later. Figs. 1 and 2 show this independence of the alterations of the T wave and of the P-R interval clearly.

DISCUSSION

With the assumption of the erect position, the arterial blood would, by gravity, be forced into the lower part of the body if certain reflexes were not active. These reflexes, which are responsible for the maintenance of the blood

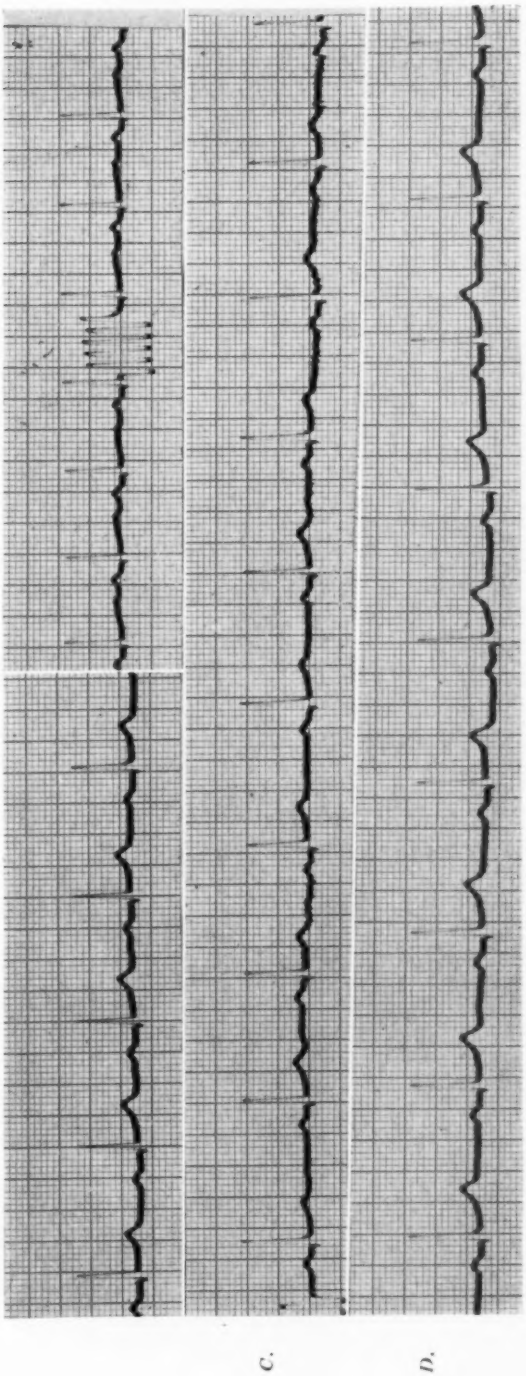

Fig. 2.—*A* was obtained in the supine posture, *B* during standing, and *C* and *D* again with the patient supine (Lead II).

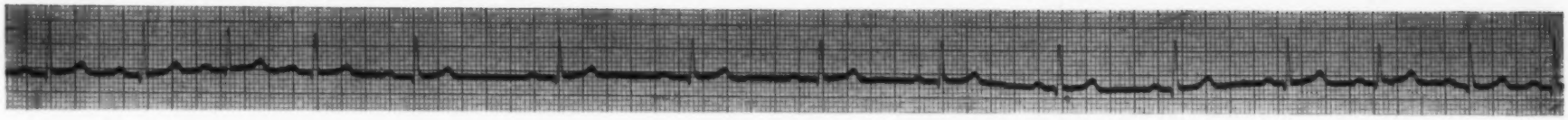

Fig. 3.—From the same patient as Fig. 2. Lead II during deep breathing and breath holding in inspiration.

A.

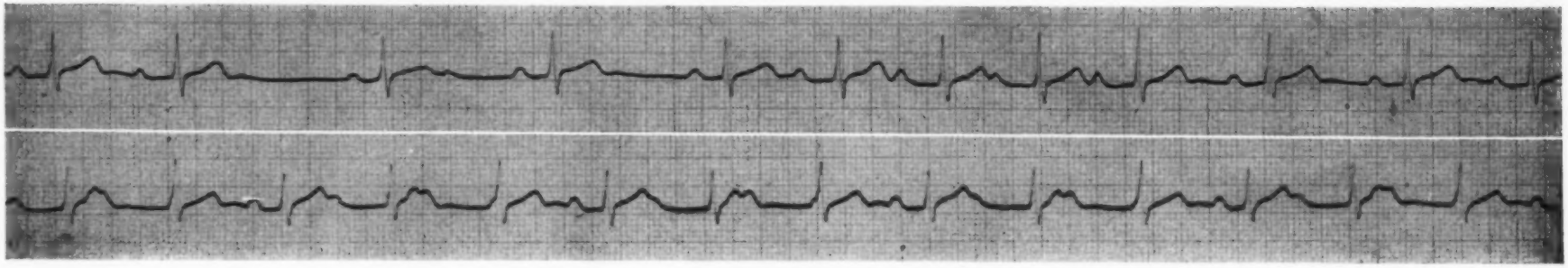

Fig. 4.—*A* shows a sinus arrhythmia and partial A-V block; *B* shows complete A-V block after administration of atropine (Lead II).

pressure by vasoconstriction, originate mainly in the receptors of the pressor nerves in the aorta and the carotid sinus. The increased rate which appears on a change from the recumbent to the upright position is attributed partly to these reflexes and partly to reflexes with afferent impulses from the thigh.[10]

The modification of the RS-T segment and the T wave on standing is due to the immediate effect of a change in the position of the heart and to different contacts between the heart and the surrounding tissue.[18] Alterations which appear later are explained by changes in the coronary circulation or by a direct influence of the sympathetic nerve system on the repolarization process.[13,17]

An increase of the sympathetic tonus and a reciprocal decrease of the vagus tonus are also assumed to be responsible for the shortening of the P-R interval in normal subjects[13] and in patients with A-V block while standing. The observation that changes in the A-V conduction time often did not appear immediately on standing, as stated in the literature, but after a short latent period, speaks in favor of the participation of the sympathetic nerves. The maintenance of the cardiac rate for a few seconds in spite of marked changes in the duration of the P-R interval is compatible with a vagal effect (loss of vagus tonus) because in some patients the sinus node does not respond to vagus stimulation while the A-V conduction time is markedly influenced. It has been observed that in certain individuals administration of even 2 mg. of atropine intravenously does not cause a change of heart rate. Actually, most of our patients showed an increase of rate only after about ten to fifteen seconds of standing, and we may assume that the immediate changes of the P-R interval might be due to vagal effect and that the later ones, which appeared simultaneously with an increase of the rate, were of sympathetic origin.

Of interest in this connection is the effect of an intramuscular injection of an ergotamine preparation on the shortening of the P-R interval caused by changes of posture.[21] DHE-45 was used in one patient in whom the P-R interval of 0.23 second fell to 0.17 second when he stood. After the administration of the ergotamine (dose not stated) the P-R interval, which was 0.25 second in the supine position, fell to 0.21 second in the standing position and after 10 minutes to 0.17 second. In another patient a P-R interval of 0.25 was measured with the patient in the supine position. When the patient stood, it fell to 0.17 and later to 0.18 second. After an intramuscular injection of Hydergin (a mixture of dihydroergocornine, dihydroergocryptin, and dihydroergocristin), the P-R interval remained 0.25 second. After he had been standing for twenty minutes, the A-V conduction time fell to only 0.23 second. In a third patient a normal P-R interval increased to 0.30 second after the injection of 1 mg. of dihydroergotamine, but when he stood, the P-R interval again immediately became normal. The influence of the ergotamine preparations on the changes of the P-R interval associated with a change of posture is, therefore, not clear.

It is remarkable that in some patients with heart block "vigorous" exercise was necessary[6] in order to accomplish a shortening of the P-R interval comparable to that seen when the erect position is assumed. In some cases (Case 9) exercise shortened the A-V conduction time more than standing with a lesser

increase of rate. From the data presented in Table I, it is apparent that in many cases the increase of rate and shortening of the A-V conduction were independent of each other. This is also evident from the experiments in which patients in the recumbent position were asked to flex the thighs and to maintain this position; according to MacWilliam,[10] this leads to an increase of rate due to afferent reflexes. In Case 28 this procedure increased the rate to the same extent as standing. While standing shortened the P-R interval from 0.24 to 0.20 second, the increase of rate caused by flexing the thigh was not accompanied by a shortening of the A-V conduction time.

The physiology of A-V conduction and, in particular, the mechanism of delay of impulse conduction in the A-V system are unknown. It is uncertain whether we are dealing with a slow transmission of the impulses in the A-V node or whether a latent period is present at the junction of the different tissues (auricular and ventricular part of the A-V node). According to the "excitation time" theory of Gilson,[5] excitation of the ventricles takes place during the time when the repolarization process of the auricular fibers is most rapid and not at the time of arrival of the auricular action potential to the ventricular border. The rapid shortening of the P-R interval in the standing position to values which are reached in the recumbent position only after appreciable exercise makes it probable that other, only partly understood mechanisms play a role in the disappearance or lessening of heart block on change of posture.

We began our study on the premise that the changes of the P-R interval with change of posture should not be immediate or permanent if a change of the tonus of the autonomic nervous system were alone responsible. Actually, our investigations demonstrated that the shortening of the P-R interval on standing and the lengthening when the supine position was reassumed appeared after a latent period between ten and fifteen seconds and that progressive changes and variations were seen for minutes. It was, however, remarkable how promptly marked changes appeared with a change of posture and how stable they were in some cases even after prolonged standing. It is difficult to explain this by considering a change of the tonus of the autonomic nerves alone.

With the disappearance of a heart block in the erect posture, one cannot infer that a "functional" or "vagal" block exists rather than one caused by actual organic changes. This conception has often appeared in the literature, and a heart block which was abolished by atropine has been repeatedly called "functional."[12] However, the response to atropine or to amyl nitrite or to changes in posture or to exertion does not permit one to separate a functional heart block caused by an increased vagus tonus from one caused by organic lesions. As early as 1922, Lewis[8] pointed out that in a patient observed by Starling in whom heart block and Stokes-Adams attacks had disappeared after atropine, the postmortem investigation revealed the presence of old organic lesions in the A-V conduction system. With the presence of such lesions, it is understandable that the addition of acetylcholine following vagus stimulation may increase the block or even make it become manifest.

We are unable to state on the basis of our relatively small group of patients why in some cases the change in posture was not associated with a shortening

of the P-R interval. It is interesting, however, that in three of the four patients in whom there was no change, a bundle branch block also existed. The bundle branch block indicated other foci of anatomical changes in the heart. It is possible that further study will reveal that nonshortening of the P-R interval on standing will permit certain conclusions as to the nature of the A-V block.

The independence of the length of the P-R interval from the duration of the preceding diastole was striking in some instances (Figs. 1 and 3). A-V conduction usually obeys the rules of rest and recovery and is shorter with a longer rest period. Exceptions are seen (type II of A-V block), and in these cases the duration of the P-R interval is independent of the length of the preceding diastole. In such patients the conduction disturbance is always due to an organic heart lesion. The effect of posture on the A-V conduction time in unequivocal cases of type II of partial heart block has to our knowledge not as yet been examined.

In many studies of the response of the P-R interval to various agents and measures, the fact that the influences are complex often seems to be dismissed. Not only are the actions of the vagus and the sympathetic nerves opposed to each other, but the action of the vagus itself may also differ. It is generally assumed that an increase of vagus tonus impairs A-V conduction. It is known, however, that the vagus does not impair conduction from fiber to fiber in the auricle and that stimulation of the vagus improves a disturbed conduction within the auricles. The new investigations on the enhancement of contraction by acetylcholine may explain these findings.

Finally, the change of the rate of the heart which usually accompanies changes of the tonus of the autonomic nervous system will also influence the rate of conduction.[9] An increase of rate caused by a higher sympathetic tonus may be accompanied by a shortening of the P-R interval because of the simultaneous effect of the sympathetic nerves on the speed of A-V conduction.[10] On the other hand, an increased number of impulses conducted per minute by the A-V system may lead to fatigue and to a slowing of the conduction. Thus, the final effect of exercise, atropine, amyl nitrite and other measures on A-V conduction is unpredictable. Fig. 4 showing the appearance of complete heart block following the administration of atropine illustrates this fact. In Case 10 standing caused a greater shortening of the P-R interval than the injection of 3 mg. of atropine.

SUMMARY AND CONCLUSIONS

1. The effect of a change from the recumbent to the upright position was studied in thirty-one patients with A-V conduction disturbances.

2. A shortening of the conduction time appeared in twenty-six patients with the change of posture from the recumbent to the upright. In many instances, A-V conduction time became normal.

3. Three of the four patients with partial A-V block who did not show any alteration of A-V conduction time with a change of posture had a bundle branch block, that is, unequivocal evidence of a lesion in the A-V conduction system.

4. It is demonstrated that the changes in A-V conduction which appear when the patient assumes the erect posture become manifest without a change

of rate and often appear after a latency of from ten to fifteen seconds. The duration of the P-R interval may vary during prolonged standing.

5. The changes of the P-R interval are independent of the alterations of the RS-T segments and the T waves.

6. The difficulties which are encountered when one tries to explain these modifications of A-V conduction by a change of the tonus of the autonomic nerves alone are discussed. The complex nature of the influences on A-V conduction is stressed.

7. The authors are of the opinion that other, as yet unknown factors may play a part in the changes of A-V conduction with an altered posture.

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ON THE MECHANISM OF THE ARRHYTHMIAS IN ABERRANT ATRIOVENTRICULAR CONDUCTION (WOLFF-PARKINSON-WHITE)

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THE subject of the Wolff-Parkinson-White syndrome[1] has received considerable attention in the recent cardiologic literature. Both its clinical and physiologic aspects are being more and more illuminated, but neither aspect is as yet clearly defined. Further observations are therefore justified. Our present report deals primarily with the arrhythmias observed in this syndrome. These arrhythmias, as is well known, give clinical significance to what otherwise would constitute merely an electrocardiographic aberration. They account for the symptoms, palpitation and dizziness, and are probably the cause of the occasional fatality recorded in the literature.

CASE REPORTS

CASE 1.—J. M., a white man, aged 53 years, one evening in July, 1948, while showering, "felt peculiar." He went to bed and awoke the following morning with a complete right hemiplegia and aphasia. In the course of several weeks he slowly recovered the use of the leg and arm and showed considerable improvement in the speech. He had complained of weakness, dizziness, and palpitation since about March, 1947. These symptoms caused him to visit the outpatient department of a number of hospitals and were the main reason for his admission to the Hospital for Joint Diseases on Dec. 2, 1948.

Physical examination revealed residual manifestations of an old right hemiplegia, weakness of the right arm and leg and right lower facial muscles. The tendon reflexes on the right side were increased, and the Babinski sign was positive. The speech was slurred.

The heart presented a regular rhythm with a rate of 72. No murmurs were audible. On x-ray examination of the chest, the left ventricle was seen to be slightly enlarged and the aortic knob somewhat accentuated. Blood pressure was 100 mm. Hg systolic and 70 diastolic. There was nothing abnormal in the rest of the physical examination. The only abnormal finding in the laboratory work-up was the presence of the Wolff-Parkinson-White syndrome in the electrocardiogram (Fig. 1). The clinical course in the twenty-six days of his hospital stay was uneventful and was marked only by a number of asymptomatic attacks of rapid and somewhat irregular heart rate discovered on routine auscultation. One of these paroxysms was recorded, and the tracing was essentially similar to the one depicted in Fig. 4, obtained at a later date.

A number of therapeutic experiments were attempted with the hope of converting the Wolff-Parkinson-White syndrome into normal sinus rhythm with normal conduction or at least of influencing the frequency of the paroxysms of arrhythmias. Neither purpose was achieved, but a number of phenomena emerged in the course of observations which throw additional light on the mechanism of the syndrome.

While the patient was on the ward on Dec. 4, 1948, a control tracing was secured (Fig. 2,*A*), and atropine sulfate 1/50 grain was administered intravenously. Two minutes later another

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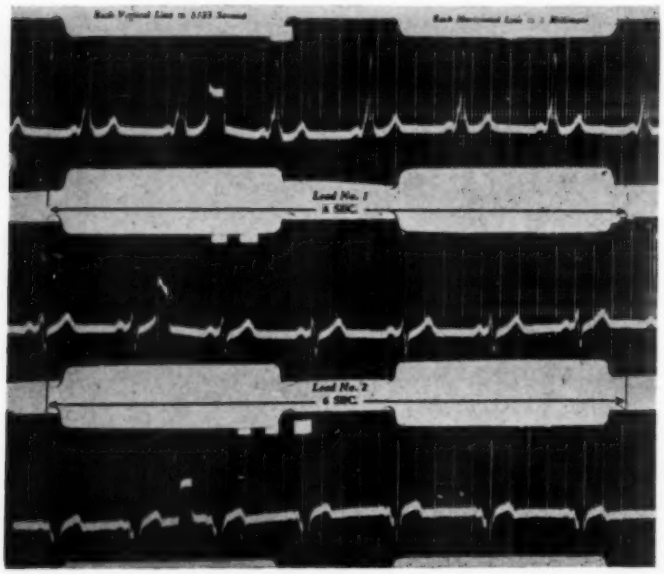


Fig. 1.—Electrocardiographic tracing of J. M. secured on admission to the hospital.

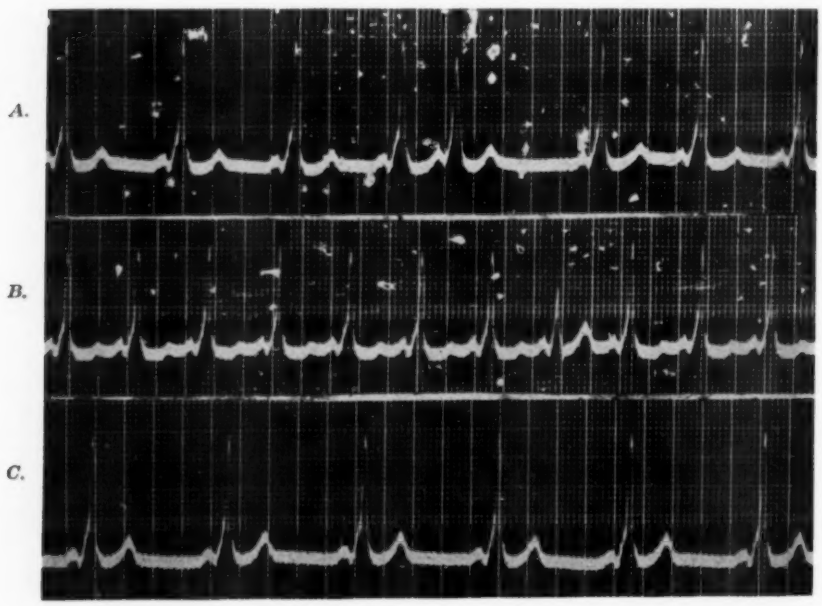
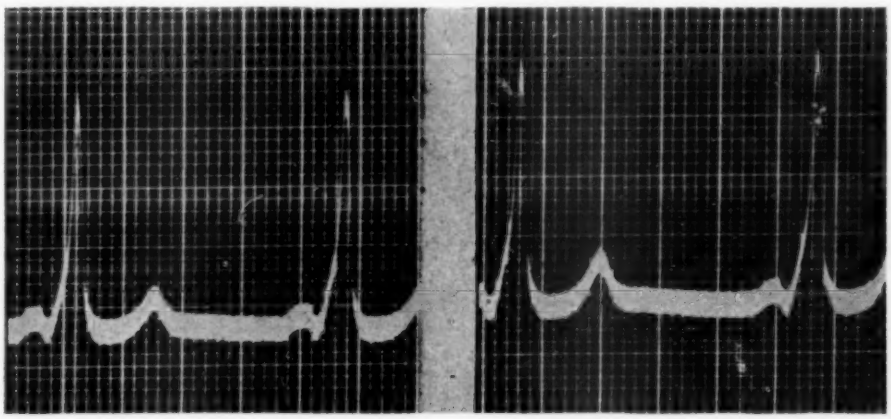


Fig. 2.—*A*, Control tracing (Lead I) secured on Dec. 4, 1948. The fifth beat is premature and is characterized by a voltage of the QRS complex lower than that of the predominant QRS complex and a lesser degree of slur on the upstroke, a phenomenon possibly due to greater influence of the atrioventricular conduction component on the resultant QRS pattern.

B, Lead I obtained two minutes after atropine sulfate, 1/50 grain, was administered intravenously. Note increase in heart rate, *narrowing* of the QRS complex, and depressed RT segment. The eighth beat in the record is probably a fusion phenomenon (see text). Note the higher voltage of the T wave.

C, Lead I obtained thirty-five minutes after 1 c.c. of 1:1,000 solution of Prostigmin Methylsulfate was administered intravenously. Note abolition of the effect of atropine. Also note the slowing of the rate beyond that in the control tracing.

electrocardiographic tracing was obtained (Fig. 2,*B*). A phenomenon described elsewhere[2] was noted. The heart rate increased, and the QRS complex, while maintaining its Wolff-Parkinson-White pattern, became *narrower*. The eighth beat in Fig. 2,*B*, while showing a short P-R interval, had a QRST complex which differed considerably from the predominant pattern and is possibly best explained as a fusion beat comprising the simultaneous conduction along both the normal and the aberrant pathways with the predominant influence of the normal conduction mechanism. Fig. 2,*C* was obtained thirty-five minutes after 1 c.c. of 1:1,000 solution of Prostigmin Methylsulfate was administered intravenously. The effect of atropine was abolished. The QRS width returned to its original value, and the sinus rate slowed even beyond that of the control tracing. The effect of Prostigmin without the intervening atropine was studied on a subsequent occasion. One cubic centimeter of 1:1,000 solution of Prostigmin Methylsulfate was administered intramuscularly after a control tracing was secured (Fig. 3,*A*). Thirty minutes later a tracing (Fig. 3,*B*) showed slowing of the sinus rate and definite although not conspicuous widening of the QRS complex.



A. *B.*

Fig. 3.—The effect of Prostigmin on the Wolff-Parkinson-White pattern without the intervening effect of atropine. *A*, Control tracing (Lead I). *B*, Tracing secured thirty minutes after 1 c.c. of 1:1,000 solution of Prostigmin Methylsulfate was administered intramuscularly. Note widening of the QRS complex.

Following his discharge from the hospital, the patient suffered frequent *symptomatic* paroxysms of arrhythmia, occurring mostly on effort. The paroxysms were due to auricular fibrillation as depicted in Fig. 4. Quinidine sulfate in varying doses up to 80 grains a day gave inconsistent results. At times, the patient would admit feeling much better and not being conscious of paroxysms, but the examiner would elicit the rapid irregularity of the apex beat. At no time was the Wolff-Parkinson-White syndrome changed to a normal electrocardiographic pattern. For a time it looked as if Atabrine was effectual in controlling the paroxysms, but, after taking the drug from March 10, 1949, to April 7, 1949, the patient decided that the medication was losing its effect. He was put back on quinidine sulfate 72 grains daily. On April 21, 1949, he came back to the clinic complaining of a "terrible night" with palpitation. It was decided to try the effect of digitalis. Digitoxin, 1.2 mg., was given in the first twenty-four hours, and a dose of 0.2 mg. was recommended as a single daily dose. On April 25 the patient stated that the new drug was the best so far, and he decided on his own to take 0.4 mg. daily. He presented no toxic symptoms. The heart rate was 70 and the blood pressure 110/70 mm. Hg; the electrocardiogram presented the usual Wolff-Parkinson-White pattern. He was warned about the possibility of toxic reaction and was ordered to discontinue the medication. The following night (April 26), according to the wife's statement, the patient suddenly developed an attack of palpitation, and, before a physician could be summoned, he died.

Pertinent electrocardiographic tracings are depicted in Figs. 4 and 5. Fig. 4 was obtained on February 17, 1949, while the patient was taking quinidine, 9 grains, three times a day. This

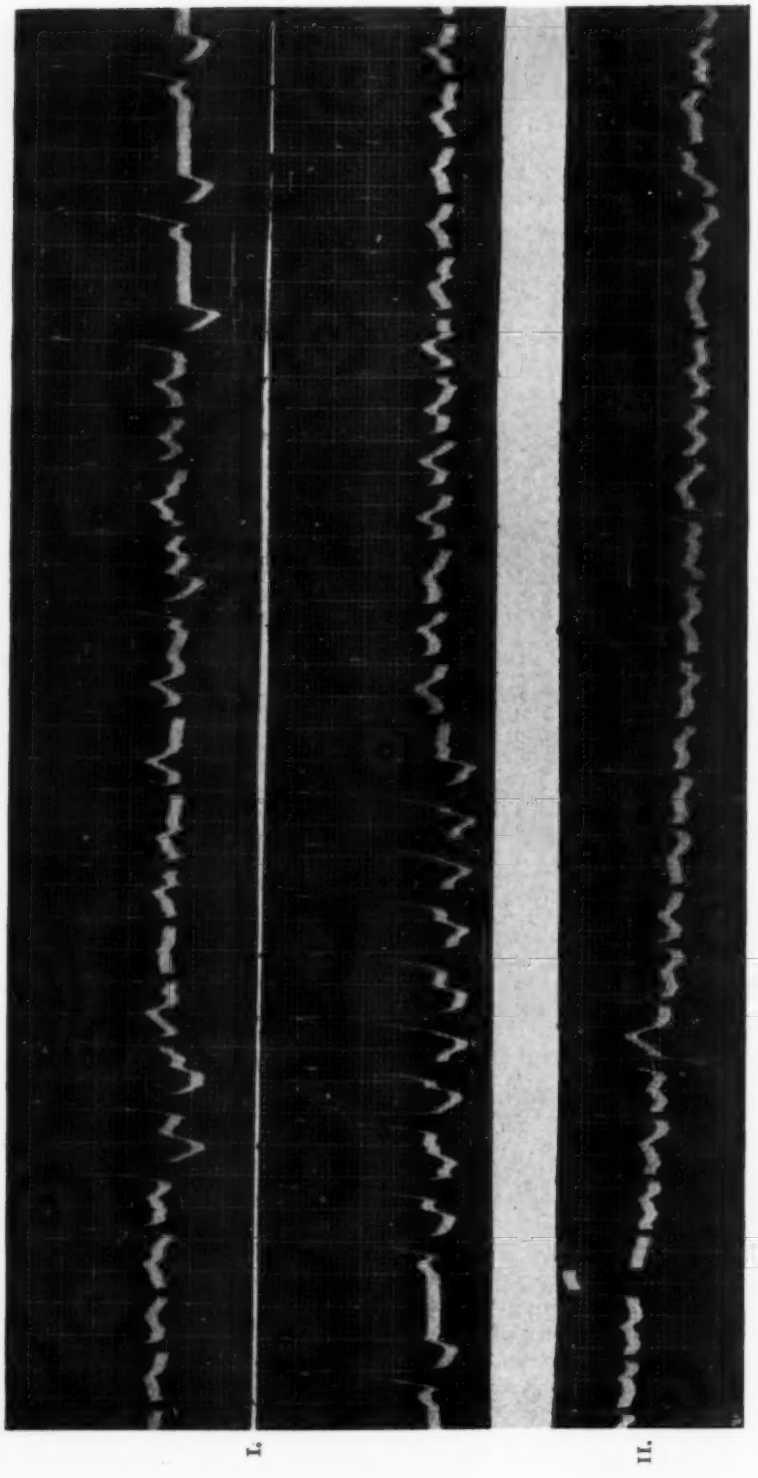


Fig. 4.—Tracing secured on Feb. 17, 1949, exemplifying the type of paroxysms J. M. was subject to. See text for description.

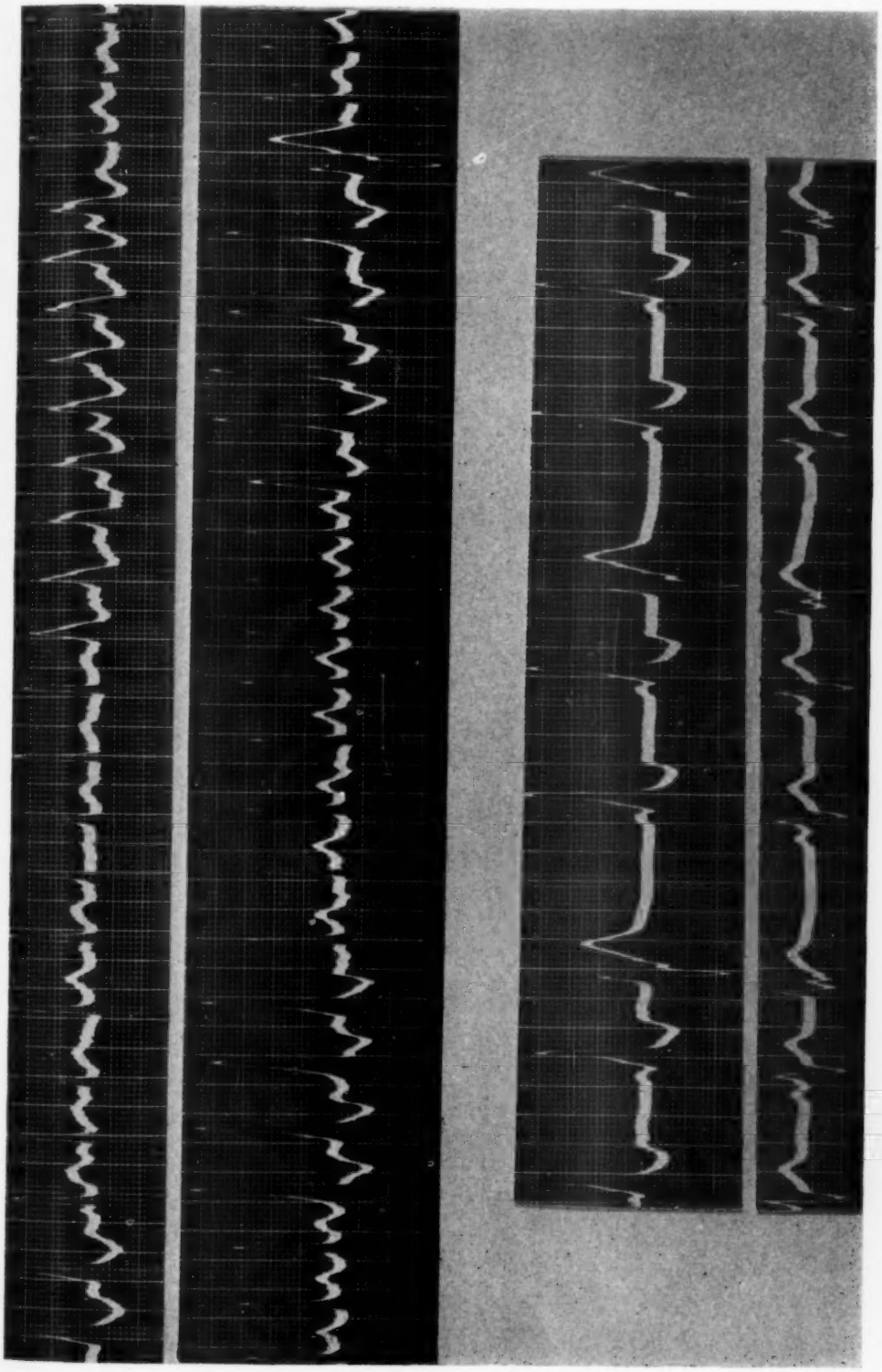


Fig. 5.—*A*, Tracing obtained on April 7, 1949 (see text). *B*, Tracing obtained on April 25, 1949 (see text).

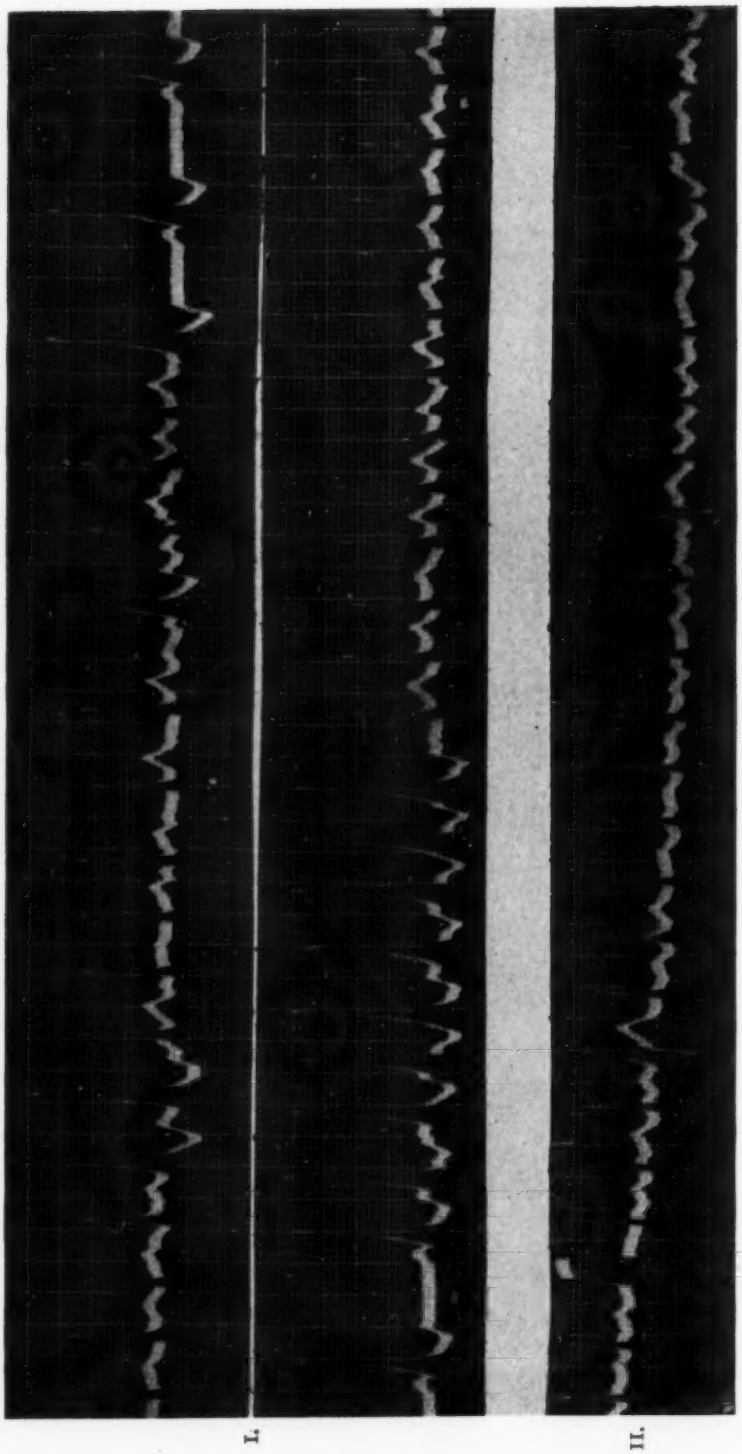


Fig. 4.—Tracing secured on Feb. 17, 1949, exemplifying the type of paroxysms J. M. was subject to. See text for description.

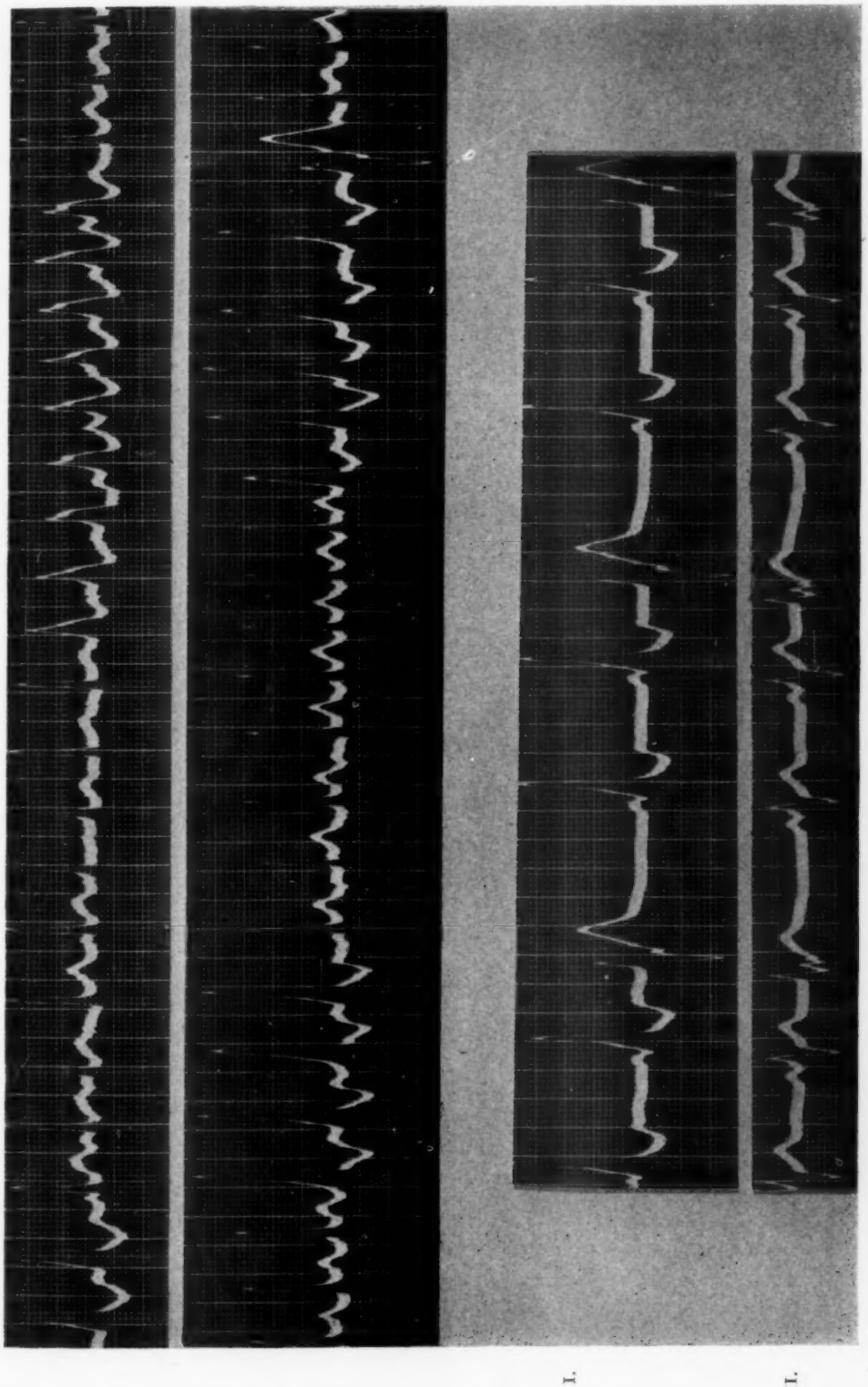


Fig. 5.—*A*, Tracing obtained on April 7, 1949 (see text). *B*, Tracing obtained on April 25, 1949 (see text).

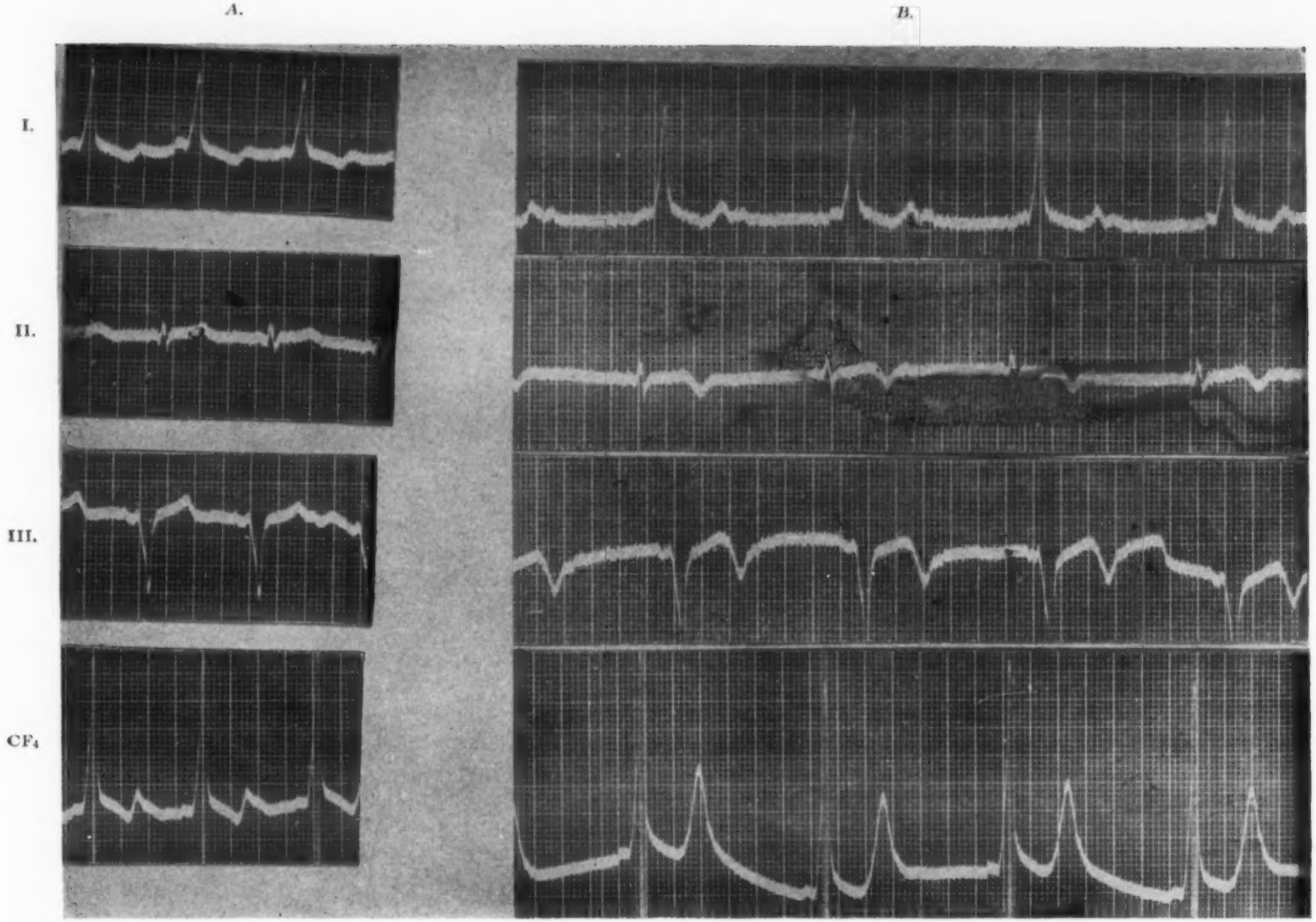


Fig. 6.—*A*, Control tracing of Case 2. Note depression of the RT segment in Leads I and CF_4. The RT segment in the Wolff-Parkinson-White syndrome is frequently unstable. *B*, Tracing secured immediately after 300 mg. of Pronestyl were administered intravenously. Note the presence of 2:1 A-V block. Also note the effect of Pronestyl on the RT segment and the form and voltage of T waves.

tracing exemplifies the paroxysms as recorded on numerous occasions. Apparently the paroxysm was one of auricular fibrillation. It is also apparent that while most of the beats were conducted through the normal atrioventricular channel, some were directed to the ventricles via the aberrant pathway. For a short while the paroxysm ceased, and the normal sinus beat was conducted regularly to the ventricles in the Wolff-Parkinson-White fashion. Fig. 5,*A* was obtained on April 7, 1949, on the day the patient decided that Atabrine lost its value. This tracing demonstrates the findings noted in Fig. 4, and, in addition, a series of nine consecutive beats probably of a fusion type and one single beat, having the characteristics of an ectopic ventricular contraction. Fig. 5,*B* was obtained on April 25, 1949, on the patient's last visit to the clinic. He was then taking digitoxin. There was now a trigeminal rhythm with an ectopic ventricular complex similar to the one depicted in Fig. 5,*A*. This arrhythmia may have been an important event. It may have served as a precursor to an attack of ventricular tachycardia and fibrillation.

Comment.—This patient with Wolff-Parkinson-White syndrome suffered frequent attacks of auricular fibrillation which could not be abolished by large doses of quinidine sulfate, Atabrine, or digitalis. There is a possibility that the patient's hemiplegia was embolic in etiology and that his death was also due to a cerebral embolus from an intra-auricular thrombus. One cannot, however, exclude the possibility of ventricular tachycardia as the cause of death. At no time during the course of observation was a normal electrocardiographic pattern secured, occurring spontaneously or as the result of drugs. The abnormal QRS complex, characteristic of the syndrome, showed, however, structural flexibility when a cholingeric drug was employed.

CASE 2.—A 70-year-old mulatto woman has been under observation in the outpatient department of the Hospital for Joint Diseases since 1943. The symptoms in the course of seven years involved various systems, but not until April, 1948, was there anything in her record pertaining to the cardiovascular system, and these symptoms consisted primarily of occasional dizziness and palpitation. In September, 1950, she had what she called a "stroke" which caused her to be hospitalized for three days in another institution. At about the same time she developed an anginal syndrome. She had no evidence of congestive failure, and the blood pressure fluctuated between 130/70 and 160/100 mm. Hg. An electrocardiogram taken in October, 1950, revealed the Wolff-Parkinson-White syndrome.

She was seen by one of us (T.T.F.) on Nov. 2, 1950, and the only finding of significance in the examination by fluroscopy was a slight enlargement of the left ventricle. The blood pressure was 130 mm. Hg systolic and 70 diastolic.

In view of the fact that Pronestyl (Squibb procaine amide hydrochloride) was reported to have some of the properties of quinidine in the control of ventricular tachycardias,[3] and also in view of the fact that the latter is known to possess the ability to convert the Wolff-Parkinson-White syndrome to a normal sinus rhythm with normal ventricular complexes, [4,5] it was decided to investigate the action of Pronestyl on the aberrant atrioventricular conduction.

On Nov. 9, 1950, after a control tracing was secured (Fig. 6,*A*), 300 mg. of Pronestyl were administered intravenously to the patient, and immediately upon withdrawal of the needle an electrocardiogram was obtained. An additional 200 mg. of Pronestyl were then given intravenously, and a second tracing was recorded. Fig. 6,*B*, obtained after the initial injection, revealed the presence of a 2:1 auriculoventricular block. Both the normal mechanism and the accessory pathway apparently failed to conduct impulses from the auricles to the ventricles.

Fig. 7 is a record of electrocardiographic events after 500 mg. of Pronestyl were given intravenously. The aberrant pathway was now considerably depressed, and the Wolff-Parkinson-White beat came through only occasionally, but a normal sinus rhythm had not made its appearance. A complete atrioventricular block ensued with an arrhythmic supraventricular QRS complex probably arising in the atrioventricular node. There was a definite time relationship between the Wolff-Parkinson-White beats and the preceding nodal complex. The aberrant beats seemed to interfere with the rhythmicity of the atrioventricular node. This was well demonstrated in the long tracing of Lead III. Longer periods of complete atrioventricular dissociation were observed with a slow, *regular* idioventricular rhythm.

syndrome is frequently unstable. *B*, Tracing secured immediately after 300 mg. of Pronestyl were administered intravenously. Note the presence of 2:1 A-V block. Also note the effect of Pronestyl on the RT segment and the form and voltage of T waves.

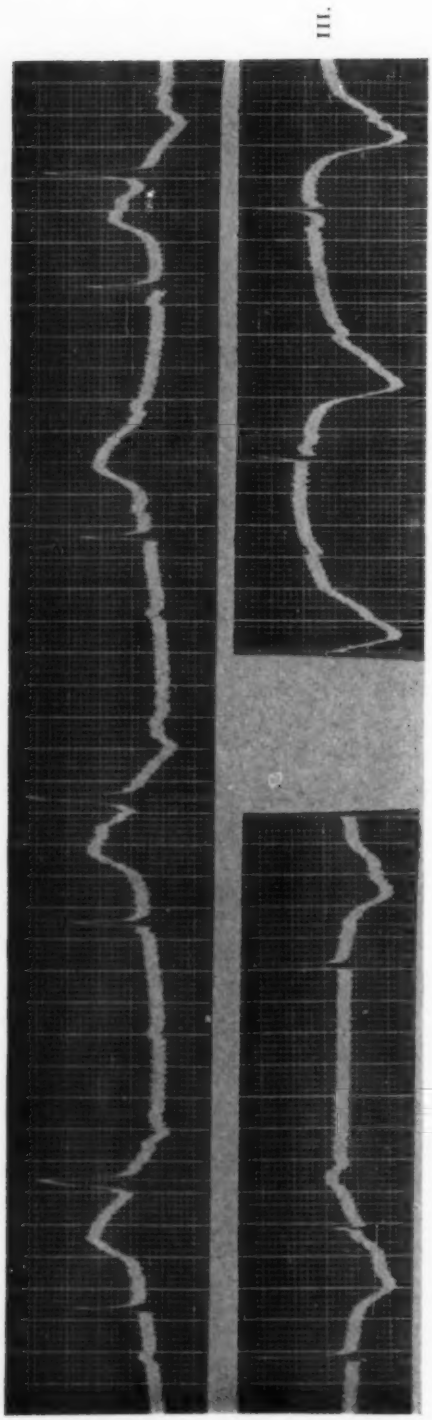


Fig. 7.—Tracing secured immediately after additional 200 mg. of Pronestyl were administered intravenously. See text for description.

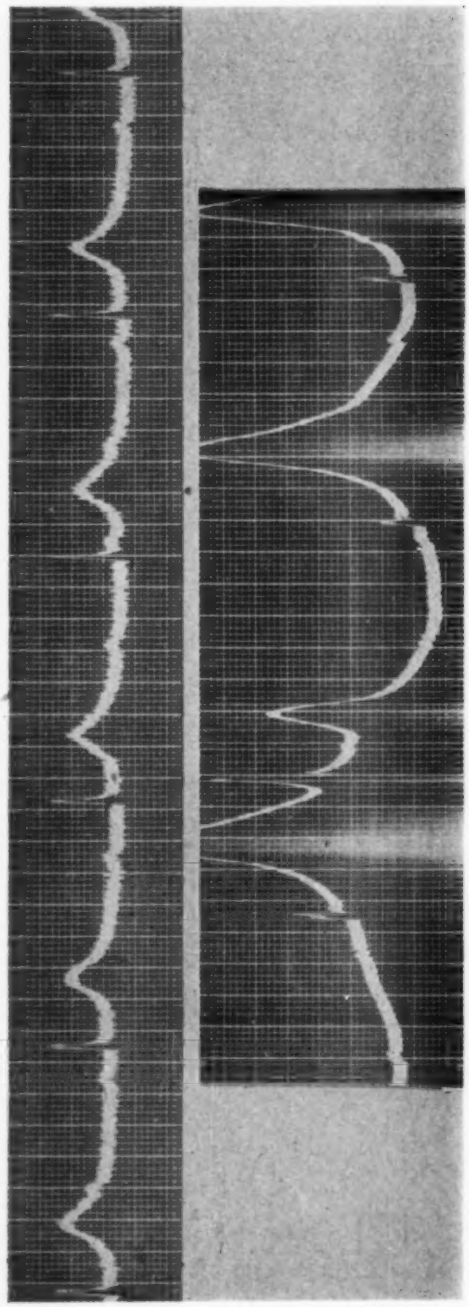


Fig. 8.—Tracing obtained five minutes after the intravenous administration of 500 mg. of Pronestyl was completed. See text for discussion.

It may be of interest to note at this point that the third Wolff-Parkinson-White beat in Lead I and the one recorded in Lead II were much narrower than those recorded in the control tracing (Fig. 6,*A*). In Lead III the Wolff-Parkinson-White beats (not recorded in Fig. 7) were of 0.08 second duration as compared with 0.12 second in the control tracing.

A tracing obtained five minutes later (Fig. 8) revealed a total absence of Wolff-Parkinson-White beats in Lead I and a regular idioventricular rhythm with a QRS complex of the supraventricular type. This effect was of short duration. When Lead III was recorded, the aberrant pathway was beginning to recover, as an occasional abnormal QRS complex made its appearance. One hour from the beginning of the experiment, a tracing secured was in every aspect similar to the one depicted in Fig. 6,*B*.

During this time the patient was asymptomatic with the exception of a brief period of dizziness following the second injection of Pronestyl. The blood pressure stayed around 130 mm. Hg systolic and 60 diastolic. She walked home, a few blocks away from the hospital, and returned two hours later. A tracing at this time showed a 2:1 atrioventricular block with QRS complexes of the Wolff-Parkinson-White type. The ventricular rate was 40 per minute. One hour later (four hours following the initial dose of Pronestyl), while an electrocardiographic tracing was being recorded (Fig. 9, Lead I), the patient suddenly became dizzy, perspired, and fainted. This state lasted a short while ("a few minutes"?) and was followed by weakness and nausea. After a brief interruption, the record was continued (Lead II, Fig. 9).

The tracing revealed the atrioventricular dissociation previously recorded. The aberrant conduction was now more frequent, but suddenly the rhythm changed to a ventricular tachycardia and to a brief period of ventricular fibrillation. This rhythm probably lasted longer than the record demonstrated. Lead II shows a 2:1 block, the predominant rhythm being disturbed by premature ventricular contractions and fusion beats.

Because of this somewhat alarming incident, the patient was admitted to the hospital. In the evening of the same day, the patient again alarmed the Staff by what appeared to be a few moments of complete cardiac standstill. The rhythm, however, spontaneously became regular, and good quality heart sounds with a rate of 80 per minute again became audible. The patient immediately felt better and was perfectly alert. No tracing of this incident was secured.

In the course of a three and one-half week period of hospital observation the patient was ambulatory and entirely asymptomatic.

Numerous electrocardiographic tracings were obtained, and all but one, recorded on the evening of admission prior to the incident of heart standstill (Fig. 10), were similar to Fig. 6,*A*. On occasions, however, for brief moments, the cardiac rhythm was disturbed. A pause would be heard on auscultation, or a slow regular rhythm would alternate with one of a faster regular quality. The brevity of these disturbances prevented their being recorded.

The effect of moderate exercise on the electrocardiogram was tested on one occasion. A 10 per cent acceleration of the sinus rate was recorded. After a three-minute rest period, a 10 per cent reduction of the rate below the control level was obtained. But an interesting and probably significant observation was made on another occasion three weeks after admission. Deep inspiration reproduced the irregularity in rhythm clinically observed on a number of occasions. For a brief period a 2:1 block was induced. After a few regular Wolff-Parkinson-White beats the 2:1 block reappeared and lasted sixteen seconds. This manifestation was strongly suggestive of a vagotonic component in the etiology of the spontaneous asymptomatic arrhythmias observed in this case.

The patient was discharged for further observation in the outpatient department. In the course of three months she had no complaints of dizziness, faintness, or palpitation. Electrocardiograms were recorded at biweekly intervals. All tracings were similar to the one depicted in Fig. 6,*A* with the exception of one secured on Feb. 16, 1951, which presented a 2:1 block in Lead I, nodal beats in Lead II, and a brief period of auricular fibrillation in Lead III. The pattern reverted to its more usual configuration when CF_4 was recorded.

Fig. 8.—Tracing obtained five minutes after the intravenous administration of 0.05 mg. of Pronestyl. All complexes

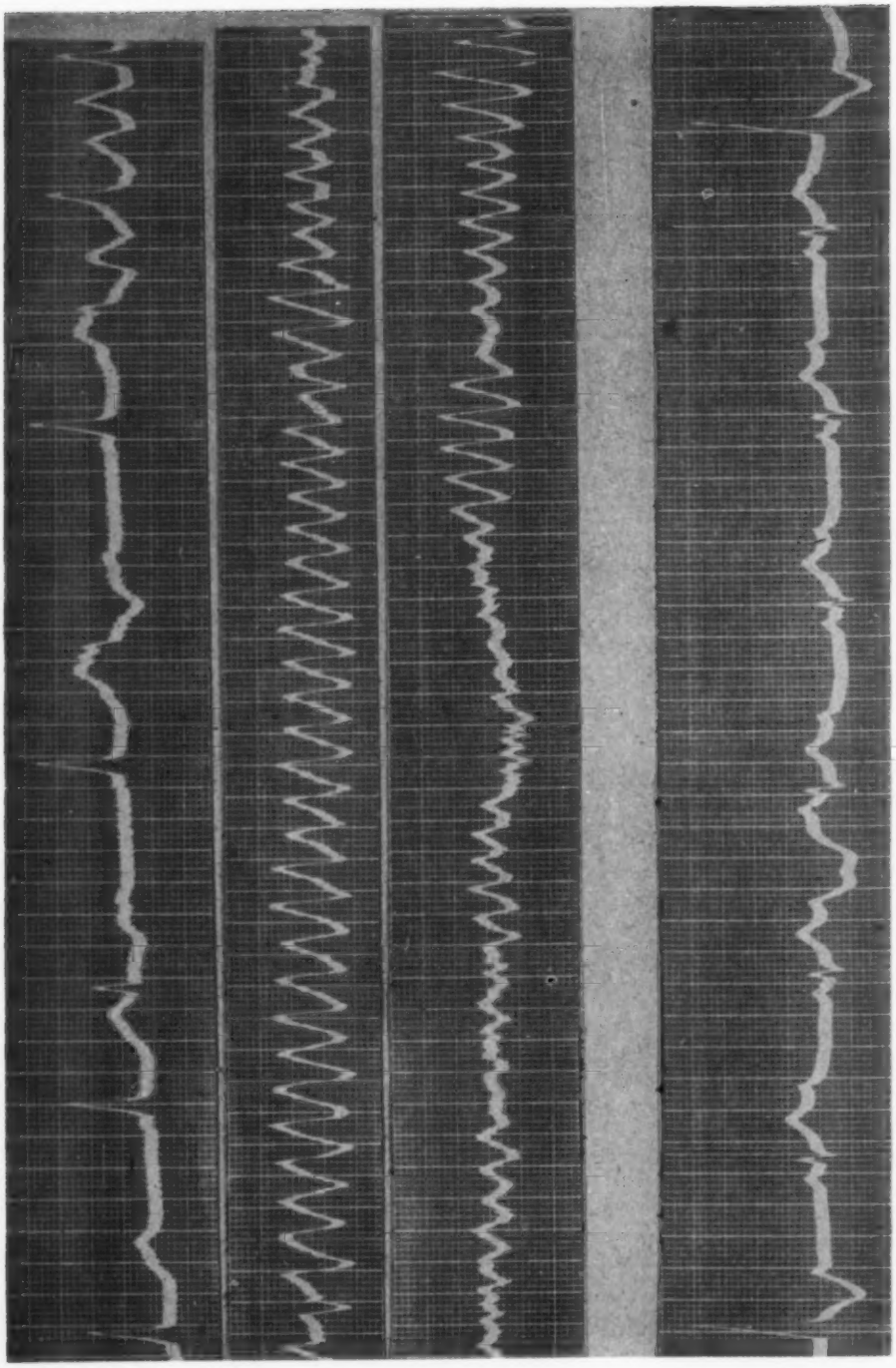


Fig. 9.—Tracing secured four hours after the initial dose of Prostyl was administered, demonstrating the presence of ventricular tachycardia and ventricular fibrillation.

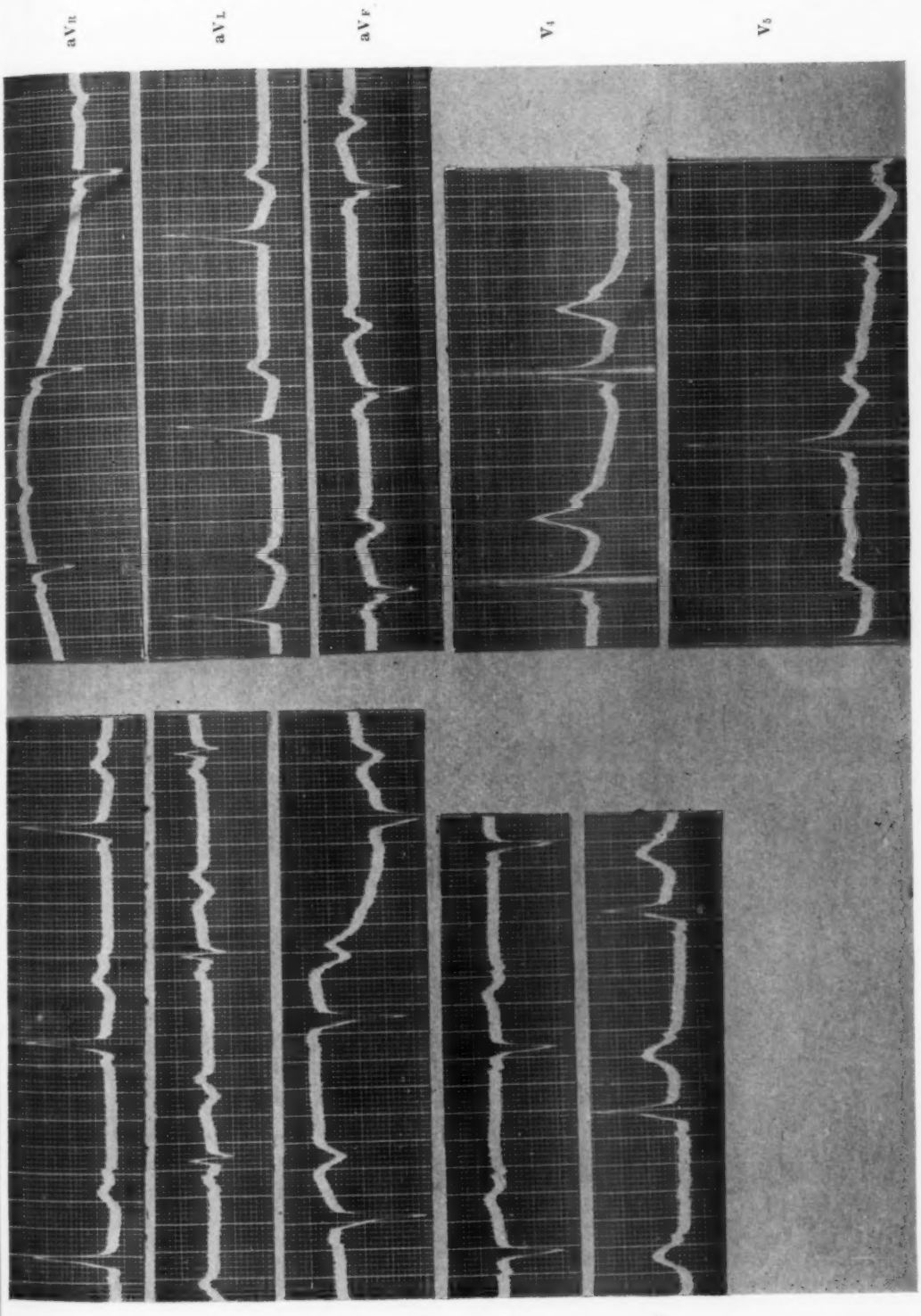


Fig. 10.—Tracing secured on the evening of admission to the hospital prior to the incident of heart standstill. Note the presence of 2:1 auriculoventricular block. Note QS in Leads III, V_1, and aV_F supposedly due to the direction of the impulse traveling from the epicardial surface of the heart toward the endocardial surface.

Comment.—This elderly patient with Wolff-Parkinson-White syndrome apparently possessed a high degree of vagus tone as manifested by the spontaneous occurrence of heart block. Pronestyl given intravenously had the effect of further depressing atrioventricular conduction, as the result of which at least one attack of ventricular tachycardia was observed. The patient was subject, in addition, to supraventricular arrhythmias in the form of nodal contractions and auricular fibrillation.

DISCUSSION

The two cases presented in this paper illustrate the occurrence of both supraventricular and ventricular arrhythmias in the Wolff-Parkinson-White syndrome. In the first case the predominant and demonstrable arrhythmia was auricular fibrillation, but ectopic ventricular beats also made their appearance on occasions (Fig. 5,*B*). Such ectopic beats have the capacity of initiating an attack of ventricular tachycardia. In the second case the significant arrhythmia was that of ventricular tachycardia, but the patient apparently at times had attacks of auricular arrhythmia, and one such paroxysm was recorded. What is the mechanism of these arrhythmias and their variations? It seems that they are "natural" phenomena of the basic mechanism of the syndrome under discussion.

The Wolff-Parkinson-White syndrome is considered to be a congenital anomaly of auriculoventricular conduction, characterized by the presence of an aberrant pathway. While usually the syndrome is manifested clinically in the younger age group, it may be dormant until senescence, when the A-V node becomes impaired and its function depressed. Thus, the syndrome seems to be dependent on the physiological integrity of the A-V node. Cholinergic drugs, such as Prostigmin or digitalis, as well as stimulation of the carotid sinus, may in some cases convert a normal rhythm with normal A-V conduction to a Wolff-Parkinson-White syndrome if an aberrant atrioventricular pathway is available. On the other hand, a myocardial depressant, such as quinidine, with a greater affinity for the aberrant pathway than for the A-V node, may so suppress the conduction along this pathway that all sinus stimuli will normally traverse the A-V node and inscribe a normal P-R interval and a normal QRS complex.

Most of the patients with aberrant atrioventricular conduction present a short P-R interval and an abnormally prolonged QRS complex. But a wide QRS complex need not be an essential criterion of this syndrome.[2] The QRS complex is really a fusion phenomenon containing two components: (1) the resultant of A-V conduction and (2) the resultant of aberrant conduction. The latter is the cause of the widening. Depression of the A-V function will cause widening of the QRS complex, as exemplified by the administration of Prostigmin Methylsulfate in Case 1, while atropine, releasing the A-V mechanism from cholinergic influences, will divert conduction from the accessory pathway into the normal channel and inscribe a narrower QRS complex. Fluctuating vagus tone may cause alternating complexes (Fig. 6,*A*).

Thus, the basic mechanism of the syndrome depends on the presence of an aberrant atrioventricular pathway and a labile functional activity of the A-V

node. The labile functional activity of the A-V node is well illustrated in Fig. 4 which shows auricular fibrillation and a series of Wolff-Parkinson-White beats. Most QRS complexes in the tracings appear to be normal, the result of normal conduction through the A-V node. This means that for a time cholinergic influences on the node have diminished. But the vagus tone soon increases, and the fibrillating auricle transmits its impulses through the aberrant pathway. The aberrant pathway apparently has a transmission threshold like the A-V node, which accounts for almost the same ventricular rate as that observed when the QRS complexes are normal. One gets the impression from this case that supraventricular arrhythmia in the Wolff-Parkinson-White syndrome depends on lifting vagus tone off the A-V node and simultaneous blocking in the lower portion of the aberrant pathway. The initiation of the fibrillation is probably dictated by the intrinsic activity of the auricular portion of the accessory pathway which acts as an ectopic auricular focus. If for a moment the accessory pathway regains its function, the already established abnormal rhythm in the auricle may transmit some of the stimuli down the ventricle in the Wolff-Parkinson-White fashion.

Incomplete depression of the functional activity of the A-V node will cause widening of the QRS complex in aberrant atrioventricular conduction. Complete functional ablation of the A-V node will give the widest QRS pattern. When, however, the A-V node and the accessory pathway are both functionally depressed, then a tracing such as depicted in Fig. 6,*A* will be recorded. If a myocardial depressant, such as quinidine or Pronestyl, which apparently exhibit affinity for the aberrant pathway, is administered, complete auriculoventricular block may be produced. Apparently that is what happened in Case 2. Ventricular tachycardia under such circumstances is a natural pathophysiologic consequence. Thus, ventricular tachycardia in the Wolff-Parkinson-White syndrome is the result of a combination of aberrant pathway block and the increase in the influence of cholinergic substances on the A-V node.

Additional comments are in order in connection with Figs. 5 and 7. The upper row in Fig. 5,*A* contains beats transmitted through the aberrant pathway, beats transmitted through the A-V node, and a series of nine consecutive beats which have the characteristics of both. Obviously they are fusion beats. Their pattern may mislead one into mistaking a supraventricular arrhythmia for a ventricular tachycardia. Such mistakes have been made in the literature. Fig. 7, in addition to the points already discussed, presents two significant findings: a markedly prolonged Q-T interval and exaggerated T-wave changes. They are caused by the action of Pronestyl. Quinidine has the same effect but to a lesser degree. The effects of quinidine on the various portions of the electrocardiogram of the Wolff-Parkinson-White syndrome have been recorded in a previous paper.[5] It seems that if a drug acts on this electrocardiographic syndrome, the effect is more marked than in normal cases. Such deep inversion of the T wave as seen in Lead III, Fig. 7, has never been recorded in the Wolff-Parkinson-White syndrome. Whether this effect is a direct toxic manifestation of Pronestyl or an expression of an electrolyte imbalance (potassium?) is difficult to say.

SUMMARY

The subject of arrhythmias in the syndrome of aberrant atrioventricular conduction (Wolff-Parkinson-White) is illustrated by two case reports. There is a possibility that one of the cases presented thromboembolic phenomena as the result of auricular fibrillation. The second case demonstrated a transient attack of ventricular fibrillation coincidental with the administration of Pronestyl.

The mechanism of the arrhythmias in this syndrome is discussed. It appears to the authors that supraventricular arrhythmias are due to lifting of the block of the A-V node and simultaneous suppression of functional activity in the lower portion of the aberrant atrioventricular pathway, that ventricular tachycardia is due to the presence of simultaneous block in both the A-V node and the aberrant pathway, and that the arrhythmias in general in this syndrome are due to fluctuations in the level of available "vagus substance."

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THE EFFECT OF INDUCED VENTRICULAR PREMATURE SYSTOLES UPON THE PRECORDIAL QRS PATTERN IN A CASE OF RIGHT VENTRICULAR HYPERTROPHY

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THERE have been two prominent schools of thought with regard to the genesis of the qR* pattern in right ventricular hypertrophy. One group of writers has stated that the qR pattern over the right precordium is due to extreme clockwise rotation of the heart, so that V leads in this area reflect chiefly potential variations of the posterobasal surface of the left ventricle.[1,2,3] Kossmann and associates[1] have presented data interpreted as indicating that the qR pattern over the right precordium in right ventricular enlargement is due mainly to left ventricular potentials and that the RS pattern seen over the left precordium is due primarily to potential variations of the right ventricle. Myers,[4] however, has stated that abnormal activation of the interventricular septum is responsible for the initial Q wave in this state.

Since the present case sheds further light on this problem and gives what is believed to be definitive evidence as to the origin of the potential variations reflected in right and left precordial leads in a case of right ventricular hypertrophy, it is thought to be worthy of a separate report.

CASE REPORT

M. T., a 46-old-old white man, had suffered from attacks of asthma with wheezing dyspnea for seven years. For six months he had had exertional dyspnea. Three to four weeks prior to hospitalization at the Veterans Hospital, Dayton, Ohio, he developed dependent edema for the first time.

He was admitted to the hospital on March 13, 1951. At this time, the blood pressure was 120/84 mm. Hg. The neck veins were distended. There were inspiratory and expiratory dry râles throughout both lungs. There were no cardiac murmurs. There were dependent edema, ascites, and hepatomegaly.

The chest roentgenogram showed pulmonary fibrosis and enlargement of the pulmonary artery, compatible with cor pulmonale. Venous pressure was 25 cm. of water; arm-to-tongue circulation time was 43 seconds. Vital capacity was 48 per cent of normal. Maximum breathing capacity was 35 per cent of the predicted normal. A clinical diagnosis of emphysema and chronic cor pulmonale was made.

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*Following the usual convention, a small letter is used to indicate a relatively small deflection, and a large letter is used to indicate a relatively large deflection.

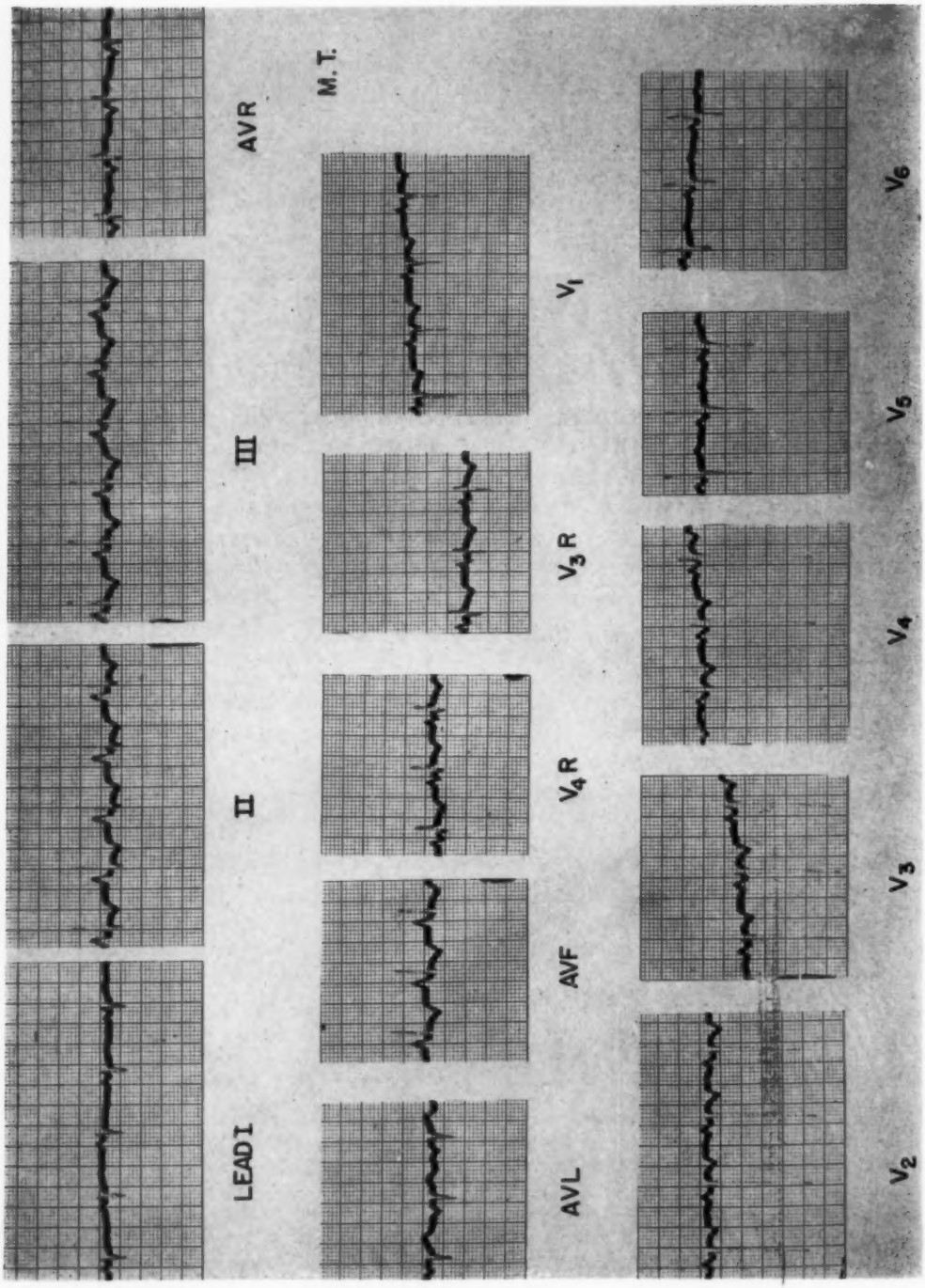

Fig. 1.—Conventional electrocardiogram of subject M. T. For discussion, see text.

The electrocardiogram is reproduced in Fig. 1. The standard leads demonstrate prominent peaked P waves and right axis deviation. Leads V_{4R} and V_{3R} show the qR complex of normal duration, characteristic of right ventricular hypertrophy, with a slightly delayed intrinsicoid deflection of 0.04 second. Leads V_5 and V_6 show an RS pattern.

Cardiac catheterization was performed on April 10, 1951, in the manner of Cournand.[6] A catheter having a wire buried in its wall but exposed at the tip was used so that intracavity pressures and intracavity electrocardiograms could be recorded simultaneously. Position of the catheter tip was verified both by fluoroscopy and by pressure curves before electrocardiograms were taken. Blood samples were analyzed in the manometric Van Slyke apparatus. Duplicate samples were required to check within 0.2 volume per cent for oxygen and within 0.4 volume per cent for carbon dioxide.

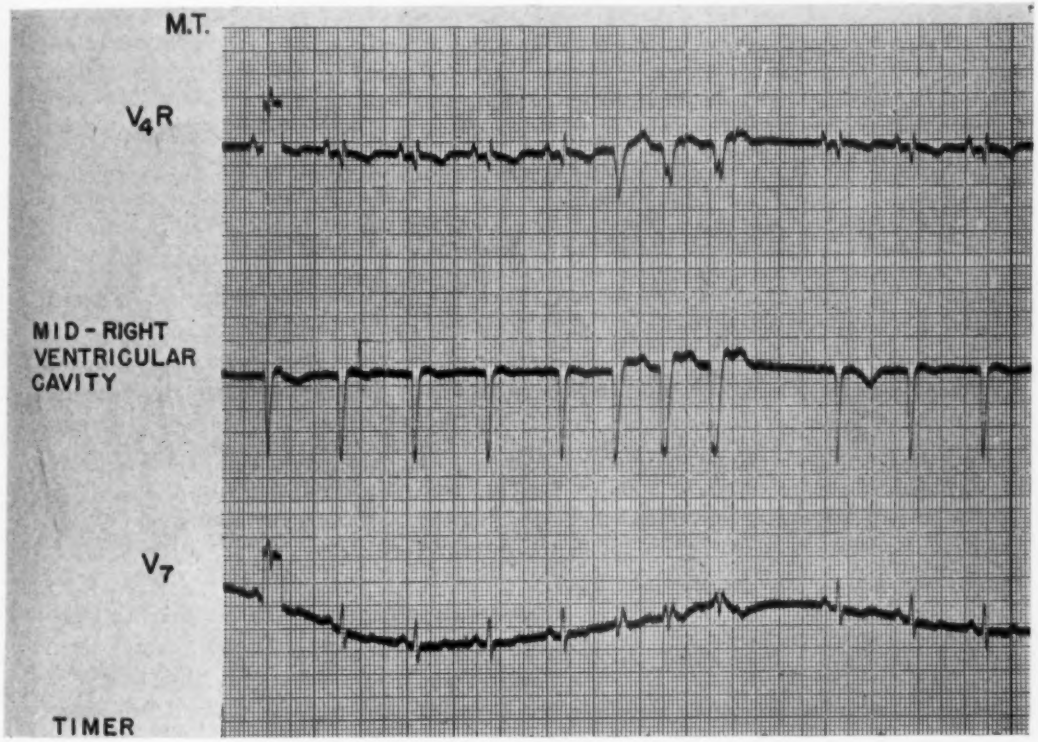

Fig. 1.—Conventional electrocardiogram of subject M. T. For discussion, see text.

Fig. 2.—Lead V_{4R}, mid-right ventricular cavity lead, and Lead V_7 recorded simultaneously. The mid-right ventricular cavity lead is recorded at approximately one-sixth normal sensitivity. Note the absence of the initial R wave in the right ventricular cavity lead. The apparent initial R wave in the first ventricular complex of the right ventricular cavity lead is due to the standardization. The sixth, seventh, and eighth ventricular complexes indicate right ventricular premature contractions initiated by irritation from the catheter tip. Note that premature contractions in V_{4R} have the same form as those within the right ventricular cavity, but that in V_7 they show an RSR′ configuration, thus indicating that Lead V_{4R} reflects potential variations of the right ventricle and that Lead V_7 reflects potential variations of the left ventricle.

Mean right atrial pressure was 10.3 mm. Hg. Right ventricular pressure was 56/12 mm. Hg. Pulmonary artery pressure was 45/27 with a mean pressure of 35.4 mm. Hg. The elevated right atrial pressure and right ventricular end diastolic pressure were interpreted as evidence of congestive failure of the right ventricle. The elevated pulmonary artery systolic, diastolic, and mean pressures were consistent with emphysema and cor pulmonale, although not so high as in other cases of cor pulmonale we have studied. The arterial carbon-dioxide content was 46.8 volumes

per 100 c.c. of blood. We have usually found this value higher in cor pulmonale due to emphysema. Arterial oxygen saturation was 83.8 per cent of capacity, a value in keeping with the emphysema. The hemoglobin was 19.5 Gm. per 100 c.c. of blood by the Van Slyke oxygen capacity method. This evidence of polycythemia is consistent with cor pulmonale and congestive heart failure.[6] During cardiac catheterization, electrocardiographic Leads V_{4R} and V_7 and the right ventricular cavity lead were recorded simultaneously, using the Technicon Triagram Cardiograph. These are shown in Fig. 2. No initial R wave was seen in the right ventricular cavity lead, either here or in the pulmonary conus region. During the strip shown in Fig. 2, three ventricular premature beats arose as the result of irritation by the catheter tip. As is to be expected, the QS configuration of the premature beats in the right ventricular cavity lead indicates that they are of right ventricular origin.[7] These three premature complexes are of similar appearance in Lead V_{4R}, except that an embryonic "R" wave may be seen in the trough of two of the S waves; this we attribute to activation of the free wall of the right ventricle. In V_7, the three premature ventricular complexes are of RSR′ configuration. The initial R wave here is attributed to the spread of depolarization through the right side of the interventricular septum. The S wave, which occurs simultaneously with the embryonic "R" wave of Lead V_{4R}, is due to activation of the free wall of the right ventricle. The R′ wave is due to activation of the free wall of the left ventricle.

DISCUSSION

In a previous report[8] we gave reasons for believing that the qR pattern in precordial leads overlying the hypertrophied right ventricle represented chiefly potential variations of the right rather than the left ventricle. During induced right ventricular premature systoles, the present case demonstrated the expected right ventricular electrocardiographic pattern of right ventricular premature contractions in Lead V_{4R} and the expected left ventricular pattern of right ventricular premature systoles in Lead V_7. To our mind this is conclusive evidence, at least in this case, that (1) Lead V_{4R} reflects chiefly right ventricular potential variations, and V_7 reflects mainly left ventricular potential variations; (2) the qR pattern in the right precordial leads is produced by activation of the right ventricle, and the RS pattern in the left precordial leads is produced by activation of the left ventricle.

Our data are in conflict with those of McGregor.[9] This author studied ten cases of tetralogy of Fallot by means of direct epicardial leads at operation and found RS patterns over the right ventricle. In our previous paper, the one case of pulmonic stenosis studied did have normal activation of the interventricular septum in contrast to five patients with cor pulmonale who had abnormal activation of the septum. This suggests the possibility that the qR complex in right precordial leads may be produced differently in cor pulmonale than in congenital heart disease.

SUMMARY AND CONCLUSIONS

There is presented a patient with right ventricular hypertrophy due to emphysema having a qR pattern in right precordial V leads. No initial R wave was seen in right ventricular cavity electrocardiographic leads. Induced right ventricular premature systoles indicated by the form assumed by the QRS complex in Leads V_{4R} and V_7 that Lead V_{4R} reflected chiefly right and Lead V_7 chiefly left ventricular potentials. The qR complex was thus thought due primarily to right rather than left ventricular activation.

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A RARE ELECTROCARDIOGRAPHIC FINDING OCCASIONALLY SEEN IN SINGLE VENTRICLE HEARTS

Report of Two Cases of Cor Triloculare Biatriatum

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THE QRS complex of the electrocardiogram has been the subject of extensive studies.[1,2] It is generally agreed that this portion of the electrocardiogram is due to the depolarization of the ventricular muscle. The complexity of the problem arises from the fact that there are, in essence, three different muscle bundles in the ventricle: those of the left ventricle, the right ventricle, and the interventricular septum. The configuration of the QRS curve depends upon the relative size of each of these muscle bundles and the direction of the wave of excitation with respect to the location of the exploring electrode.

A single ventricle heart, with either one or two atria, is one which lends itself to the study of the electrocardiographic findings with respect to the ventricular complex. The complete absence of a septum or the presence of only a miniature or rudimentary septum converts the ventricles into a single muscle mass. A study of the tracings obtained from such hearts should throw light on the subject.

Taussig,[3] in discussing the electrocardiographic findings in the single ventricle heart, stated: "Although the course of the bundle of His must be grossly abnormal, it is a striking fact that there may be no demonstrable disturbance of the intra-ventricular conduction time; the QRS complexes may be entirely normal." The cases to be reported below present an unusual similarity of precordial ventricular complexes which, when present, may be suggestive of the condition.

There are six possible situations in which the ventricle is essentially a single muscle mass. There is the true single ventricle in cor biloculare or in cor triloculare biatriatum. In the former, a single atrium empties its blood into the solitary ventricle, and in the latter the blood from both atria flows into the single ventricle. A third type is that in which one ventricle is rudimentary in character, the interventricular septum consisting merely of a ridge of muscle, the rudimentary chamber receiving only a small part of the blood. Functionally, there is one predominant muscle mass. Another type of single ventricle is that in which one ventricle is buried within the wall of the other. Tricuspid atresia and mitral atresia, because of the underdevelopment of their respective ventricles, also result in functional single ventricle hearts.

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We have had an opportunity of studying two patients in whom a single ventricle was present. One of these patients is still alive, and the diagnosis of single ventricle was confirmed after operation.[4] In the other it was confirmed at necropsy.

Since the single ventricle does not contain a septum, theoretically no transition zone should be seen on the electrocardiogram. We therefore have studied the patient who is still alive by recording leads completely around the chest. The results of these studies will be discussed later.

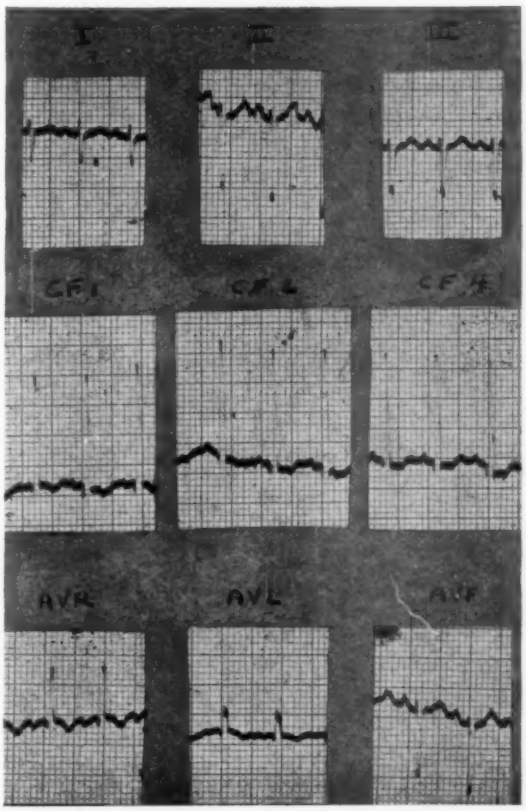

Fig. 1 (Case 1).—Electrocardiogram showing the main deflections downward in the standard leads. Limb leads show aV_R to be the mirror image of aV_F with the heart in the horizontal position. Precordial Leads CF_1, CF_2, and CF_4 are similar in outline, and their intrinsicoid deflections are equal to one another. High R waves are seen in aV_R and in CF_1.

CASE REPORTS

CASE 1.—R. V.,* a 4-week-old male child, had a normal birth. At the age of 3 weeks cyanosis was observed. This disappeared during crying. The child was well developed, and there were no other external manifestations of any developmental abnormalities. On examination of the heart, the rate was found to be 170 per minute and regular. The heart was not enlarged. No murmurs were heard, and no thrill was palpable. Moderate general cyanosis was present.

*This case was referred to one of us (A.W.F.) by Dr. Morris Wein.

The electrocardiogram (Fig. 1) showed a sinus tachycardia with a rate of 170. Small r and deep S waves were present in all three standard limb leads. The T waves were upright. The entire ventricular complex in the standard limb leads consisted of two deflections, an rS. The augmented unipolar limb leads also showed two deflections in the ventricular complex. In aV_R and aV_L, it consisted of a qR and, in aV_F, of an rS. The main deflection in each of the limb leads was notched at the peak. aV_F and aV_R were inverted images of each other. The precordial leads (CF_1, CF_2, and CF_4) resembled one another and consisted also of two deflections.

Two weeks later the child died suddenly, and a post-mortem examination was performed. The pertinent findings were limited to the heart which was moderately enlarged. On external examination, an apparent transposition of the great vessels (Fig. 2) was noted. When the heart was opened, the right and left atria were shown to be normally developed and separated by a septum which terminated just above the atrioventricular ring (Fig. 3), leaving a free unattached inferior border. Within this septum could be seen the closed foramen ovale. The atrioventricular ring consisted of five well-formed cusps, separating the two atria from a large single ventricle. The aorta was found to arise from this single ventricle. On the upper right surface of the ventricle and to the left of the aorta was a ridge of muscle, which, with the wall of the ventricle, formed a small entrance to a rudimentary chamber (Fig. 4) which communicated with the pulmonary artery. The combined right and left atrial blood emptied into the ventricle, which, in turn, propelled the blood to the aorta and, by way of the rudimentary chamber, to the pulmonary artery.

This is, therefore, a true case of cor triloculare biatriatum with two well-defined atria, a single large ventricle, and a rudimentary chamber.

CASE 2.—R.M.,* a 3-year-old white boy, was first examined in July, 1948, because of marked dyspnea and cyanosis. He was the second child of a 32-year-old housewife. The delivery had been normal with birth weight of 6 pounds, 13 ounces. A marked cyanosis noted at birth had persisted until the present examination. The development had been delayed. He sat up at one year, stood at 17 months, and started to walk at 2 years. He did not squat.

On examination the boy was small and underweight. Marked generalized cyanosis was present. The fingers and toes showed advanced clubbing. Dyspnea, which was moderate at rest, became extreme when the child cried.

The heart was greatly enlarged downward and to the left, the point of maximum impulse being felt in the sixth intercostal space at the anterior axillary line. No thrill was palpated. An inconstant, soft, systolic murmur of variable intensity was heard over the second left intercostal space.

Fluoroscopic examination in the posteroanterior view showed an aneurysmal dilatation in the region of the outflow tract of the right ventricle. There were forceful pulsations of this shadow, yet the lung fields were quiet and showed few markings. In the right anterior oblique view the heart bulged abruptly toward the anterior chest wall, forming a sharp angle with the ascending aorta. The incisura was absent.

Repeated electrocardiograms (Fig. 5) showed sinus rhythm with marked left axis deviation and the heart in the horizontal electrical position. There was no delay in conduction. The P deflections were large in the standard limb leads and in V_2 and V_4. They were inverted in aV_R, V_1, and V_{4R}. The ventricular complex in aV_R consisted of a very small q and a tall R deflection. The T waves were inverted in Leads I, aV_R, and aV_L and upright and large in Leads II, III, and aV_F. aV_F was the mirror image of aV_L. In all the precordial leads T was upright.

The precordial leads were unusual in that the main deflections were negative and similar in form, although varying in voltage in all leads encircling the chest. The QRS complexes consisted of deep QS or rS waves.

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*This case was referred to one of us (G.B.N.) by Dr. H. Robert Kutil.

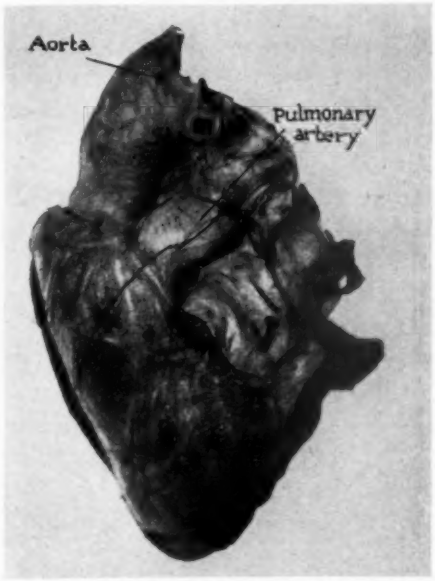

Fig. 2 (Case 1).—Photograph of anterior aspect of heart showing the position of the great vessels.

Fig. 3.

Fig. 4.

Fig. 3 (Case 1).—The opened heart showing the unattached free lower margin of the atrial septum and a common atrioventricular valve consisting of five cusps.

Fig. 4 (Case 1).—The opened heart showing the entrance to the rudimentary chamber from the common ventricle.

On entering the ventricle during catheterization,* the tip of the catheter was seen to pass directly to the left border of the cardiac shadow, suggesting the diagnosis of a single ventricle. Further examination at that time was unsatisfactory because of the child's condition.

He was referred to the service of Dr. Helen B. Taussig for anastomosis of a subclavian artery to the pulmonary artery. This was performed in March, 1951. The final report confirmed the diagnosis of single ventricle heart.[4]

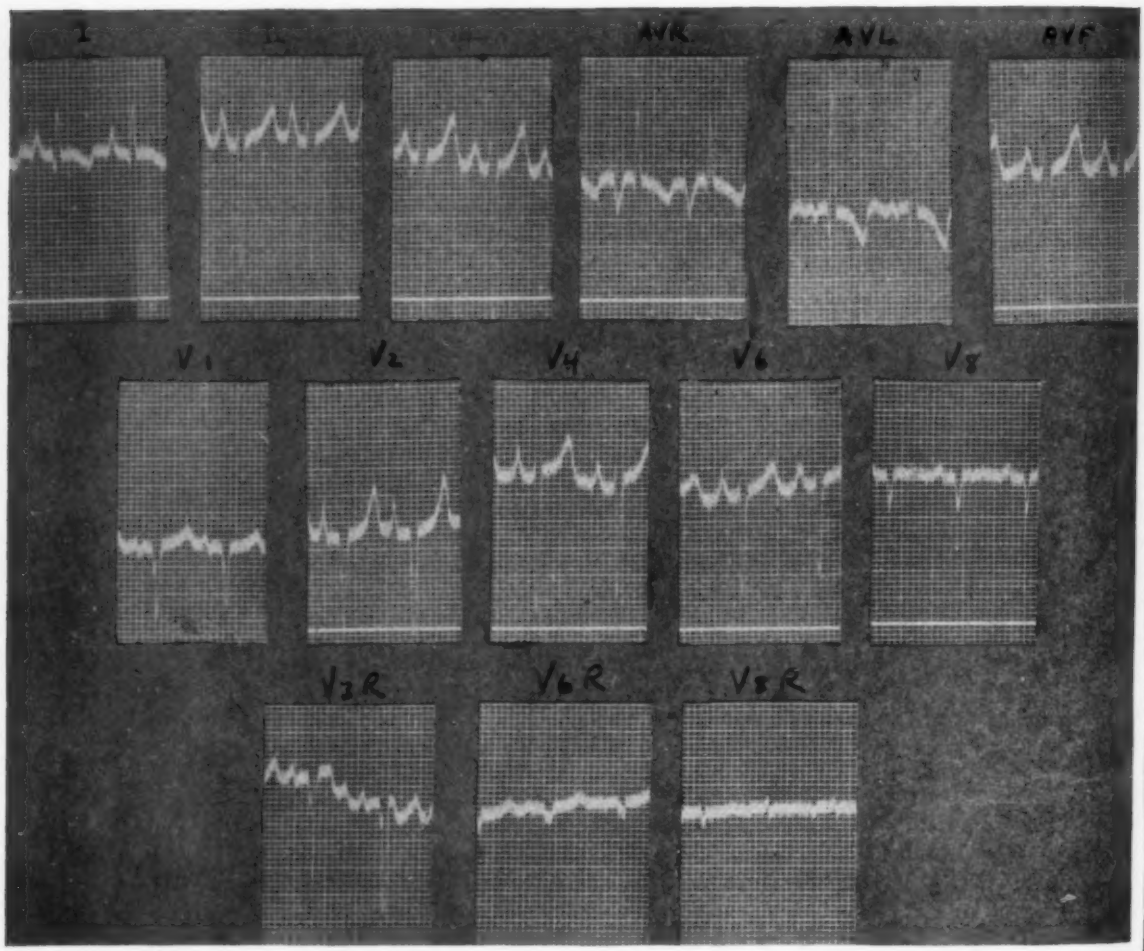

Fig. 5 (Case 2).—Electrocardiogram showing left axis deviation with vertical electrical position of the heart. P waves are large in standard Leads aV_F and V_2. The QRS-T curves in aV_L and aV_F are mirror images of each other. The precordial leads encircling the chest show ventricular complexes of similar downward direction.

At the present time (six months after operation) the child has improved, and his exercise tolerance has increased greatly. His appetite is better; he is sleeping well, and he has started attending school.

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*Performed at the cardiorespiratory laboratory of St. Luke's Hospital by Dr. Robert Nims.

DISCUSSION

Gardberg and Ashman[1] have demonstrated that the first portion of the normal ventricle to be stimulated is the left side of the interventricular septum by a twig from the left branch of the bundle of His. Since there is no true interventricular septum, depolarization of this part of the ventricle and its contribution to the inscription of the QRS are absent. The course of the bundle of His must be abnormal. Despite the obviously unusual path taken by the bundle and its branches, neither of our patients exhibited heart block nor disturbances in bundle branch conduction. Brown[5] discussed the work of Mall,[6] Tandler,[7] and Monckeberg[8] with reference to the state of the bundle of His in malformations of the septa: "The salient feature that emerges from this work is that the development of the septa takes place after the development of the bundle and thus it seems unlikely that malformations of the septa will interfere with the development of the bundle that has already appeared."

The absence of a true interventricular septum further separates such hearts from the normal in that there is no differentiation in muscle masses of right and left ventricles. This also tends to exhibit its effect on the electrocardiogram. The exact path taken by the bundle in our patients is unknown. Wilson and Grant,[9] by means of serial sections, were able to demonstrate the path of the conduction system in their patient.

Brown[5] stated: "In complete absence of the interventricular septum the bundle may be found running along the tag of the rudimentary septum and, even in the cor biloculare, it has been found on the posterior wall of the common ventricle, dividing into right and left branches." If the bundle runs in the rudimentary septum and divides into two branches, the relative proportion between the main ventricle and the rudimentary one is such that the effect on the electrocardiogram of the latter would be negligible. If it runs on the posterior wall of the common ventricle and divides into two branches there, then the entire ventricular mass is stimulated from the same source, and a single accession wave is traveling over the lone ventricle. The electrical axis of the single ventricle may then be either right or left or undetermined. The precordial leads, taken from different sites on the chest at the same level, would have the same configuration. No transition zone should be present, and, as shown in Case 2, leads taken from points completely encircling the chest show no such transition zone. In this connection the level at which the electrodes are placed is very important. If placed too high, the electrode will face the cavity of the heart and show variable tracings.

The unipolar limb leads are extremely interesting. In Case 1, the left leg lead is the inverted mirror image of the right arm lead, while in Case 2, the left leg lead shows a similar relationship with the left arm lead. This is probably due to the different electrical position of the single ventricle in relation to the extremities.

The ventricular complexes in all the leads consist of only one or two deflections, a qR, Rs, QS, or R. In neither of the tracings is there a QRS curve of three deflections. This again may be due to the absence of the interventricular

septum as well as to the absence of differentiation in the size of the muscle mass from either side of the heart.

SUMMARY AND CONCLUSIONS

A study of the ventricular complex in hearts with a single ventricle should throw light on the mechanism of production of the QRS complex. Two cases of such a condition are described, and the electrocardiographic findings are discussed. When present, this unusual electrocardiographic finding may offer a simple diagnostic sign of single ventricle heart.

The authors are indebted to Miss Bernice Nicolson for the drawings in Fig. 3 and Fig. 4.

ADDENDUM

Since this article was written a case of a 6-month-old infant with pseudo cor triloculare (tricuspid stenosis and pulmonic atresia as disclosed by post-mortem examination) has come to our attention. Electrocardiographic findings in this case show similar QRS complexes in the six usual precordial positions. The unipolar limb Leads aV_L and aV_F are mirror images of one another.

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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF ACUTE COR PULMONALE

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THE diagnosis of acute cor pulmonale by electrocardiographic methods has been greatly enhanced by the use of unipolar precordial and augmented extremity lead recordings. The electrocardiographic criteria were formerly based upon the three standard and one or two bipolar chest leads. They consisted of the development of a prominent S_1, with depression of the S-T segments in the standard Leads I and II, associated with a "staircase" ascent and a conspicuous Q_3 with late inversion of T_3.[1] Other changes considered of diagnostic importance were transient right bundle branch block,[2] inversion of the T waves in one or more bipolar chest leads,[3] and the presence of tall, peaked P waves in Leads II and III.[4] In one study[5] in which these "classic" patterns were employed as criteria, it was reported that the typical electrocardiographic changes described by McGinn and White[1] in acute cor pulmonale were found in only 10 per cent of cases of pulmonary embolism.

Since the advent of unipolar electrocardiography, additional criteria for the diagnosis of acute cor pulmonale have been described. Wilson and associates[6] demonstrated shift of the interventricular transitional zone to the left. Goldberger[7] described shifting of the heart toward the vertical position in association with clockwise rotation. Other workers[8] observed patterns of acute coronary insufficiency following acute pulmonary embolism, especially in previously damaged hearts. In a recent series of cases of acute cor pulmonale confirmed at autopsy, Phillips and Levine[9] showed the importance of the electrocardiogram as a means of early and accurate diagnosis. They considered inversion of the T waves in one or more precordial leads, shift of the transitional zone to the left, and the occurrence of incomplete right bundle branch block as the significant criteria.

The group to be reported consists of eight patients with pulmonary embolism or pulmonary infarction, six of whom were observed at the San Francisco Hospital (University of California Service) and one (Case 5) at the Veterans Administration Hospital (Fort Miley); the other (Case 2) was a private patient seen in consultation at the Doctors Hospital, San Francisco. By taking augmented extremity and unipolar precordial leads, in addition to the three standard leads, it was possible to detect electrocardiographic changes indicative of acute cor pulmonale in all eight patients. The analysis of the multiple lead tracings also assisted in clarifying the mechanism of production of the patterns that had been observed in the three standard and one or two bipolar records.

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In four patients, control electrocardiograms were obtained before the attack and were compared with tracings taken after the embolism occurred. In the remaining patients, records were obtained sufficiently soon after the attack to reveal subsequent serial changes of diagnostic value. In all cases the occurrence of pulmonary embolism or infarction was verified by well-defined clinical signs, roentgenographic evidence, or pathologic material. The various postembolic electrocardiographic changes were considered as "early" if they occurred within several hours of the attack and "late" if they appeared more than twenty-four hours after it.

TABLE I. ELECTROCARDIOGRAPHIC FINDINGS IN ACUTE COR PULMONALE

	TOTAL	EARLY	LATE
Transitional zone shift to left	8 (100%)	7	1
Cardiac rotation (clockwise and vertical)	6 (75%)	6	0
Apex forward, 3 cases			
Apex backward, 3 cases			
Coronary insufficiency (myocardial anoxia)	4 (50%)	2	2
Right ventricular strain (T inverted in V_{1-4}, V_5, or V_6)	4 (50%)	3	1
Auricular arrhythmias (fibrillation and/or premature beats)	3 (37.5%)	0	3
Right auricular dilatation (P-pulmonale)	2 (25%)	0	2
Right bundle branch block (transient)	1 (12.5%)	1	0

Three standard leads, three augmented extremity leads, and six (V_1 to V_6) unipolar precordial leads were taken on every patient, employing the method recommended by the American and British Heart Associations.[10]

In the eight patients studied, the observed changes, in order of frequency, were as follows:

1. *The shift of the transitional zone to the left (8 cases)* was determined primarily by observation of reciprocal deepening of S waves and diminution of the amplitude of R waves in Leads V_3 to V_6 in serial records (Fig. 1). In several instances a return to the basic pattern occurred some days later, at the time of resolution of the pulmonary infarction. This occurred as an early change in seven of the eight cases.

2. *Cardiac rotation occurred in 6 cases.* An increase of the vertical position of the heart was associated with forward displacement of the apex in three patients and with backward displacement in three, in accordance with the criteria of Goldberger.[7] In all cases it was accompanied by clockwise rotation.[7] The degree of rotation was greater in the younger patients and in those in whom there had been no basic pattern of left ventricular hypertrophy before the pulmonary embolism.

3. *Coronary insufficiency* as an indication of myocardial anoxia occurred in four cases. This abnormality was uniformly observed in those patients in the older age group who had preexistent coronary artery sclerosis or left ventricular hypertrophy and occurred equally often as an early and a delayed change (Fig. 2).

4. *Right ventricular strain* was evident in three patients as an early change and once as a delayed change. This pattern was manifested by an extension of the inversion of the T waves in precordial Lead V_1 as far to the left as V_4, V_5, or V_6 (Fig. 3). Changes resulting from a shift toward a more vertical position of the heart and clockwise rotation occurred concomitantly. Previous cardiac disease was not usually present.

5. *Auricular arrhythmias*, appearing as premature contractions or auricular fibrillation, were observed in three patients as a delayed abnormality. In each instance the arrhythmia was associated with one or more of the patterns described previously.

6. *Right auricular dilatation,* shown by the classic P-pulmonale, was noted in two patients as a late manifestation. In both cases it occurred in conjunction with the more basic changes of a shift of the heart toward the vertical position and clockwise rotation.

7. *Right bundle branch block* was found in one patient. It occurred early in the attack and was of a transient, incomplete nature; its disappearance was followed by electrocardiographic evidence of a significant leftward shift of the transitional zone within twenty-four hours of the acute episode.

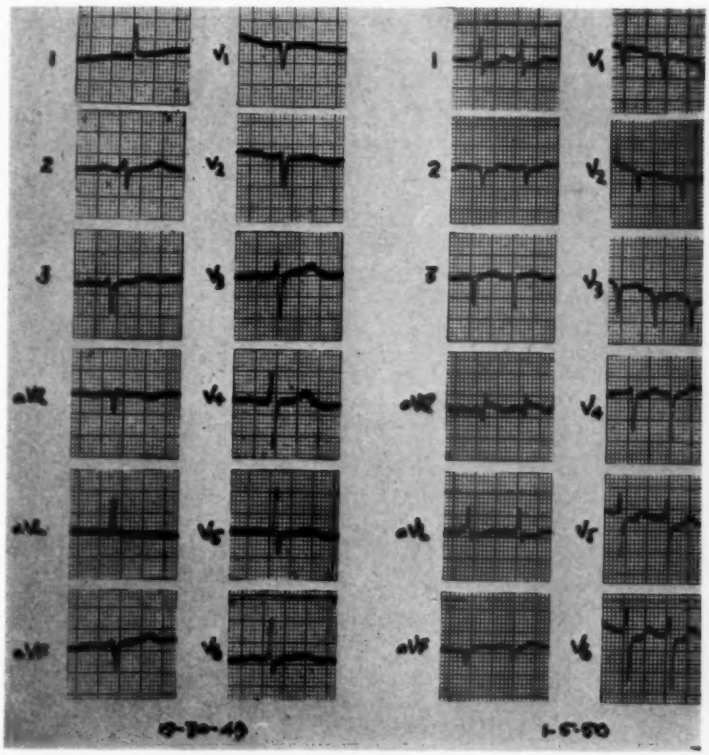

Fig. 1.—Electrocardiograms taken before and after the occurrence of a massive pulmonary infarction that terminated in death six hours after the second tracing. Record of Dec. 30, 1949, reveals the heart in a horizontal position, with sinus rhythm and prominent S_{V1-6}. The aV_R deflection is predominantly downward. Record of Jan. 5, 1950, shows auricular fibrillation, shift of the transitional zone to the left with deep S_{V1-6}, depressed S-T segments in V_5 and V_6, and a prominent upward deflection in aV_R. Leads I and II show a "staircase" ascent of the S-T segments.

CASE REPORTS

CASE 1.—A. L., a 69-year-old woman, was admitted to the San Francisco Hospital on Dec. 29, 1949. During the last ten years she had experienced pain, swelling, and tenderness of the left leg, with an exacerbation immediately prior to hospitalization. Symptoms of hypothyroidism had been present for the past three years. Physical examination revealed an obese, elderly woman with a hoarse voice who presented clinical signs of myxedema. The lungs appeared normal. The blood pressure was 180/100 mm. Hg and the pulse rate 64 per minute. The heart sounds were normal. Venous obstruction with ulceration of both legs was present. The blood cholesterol level was 300 mg. per 100 cc. The basal metabolic rate was −38 per cent. On Jan. 5, 1950, the patient became acutely dyspneic and cyanotic, but did not complain of pain. The blood pressure fell to 165/70 mm. Hg as auricular fibrillation with a ventricular rate of 120 per minute appeared. Consolidation of the lower lobe of the right lung became evident, and the patient died within eight hours of the onset of the attack.

Comment.—The serial electrocardiograms on the patient (Fig. 1) illustrate the electrocardiographic changes that followed a major acute pulmonary infarction, with the development of an auricular arrhythmia and rotation of the electrical position of the heart in a clockwise direction with posterior displacement of the apex. In addition, there was evidence of myocardial anoxia. These changes occurred within two hours of the attack.

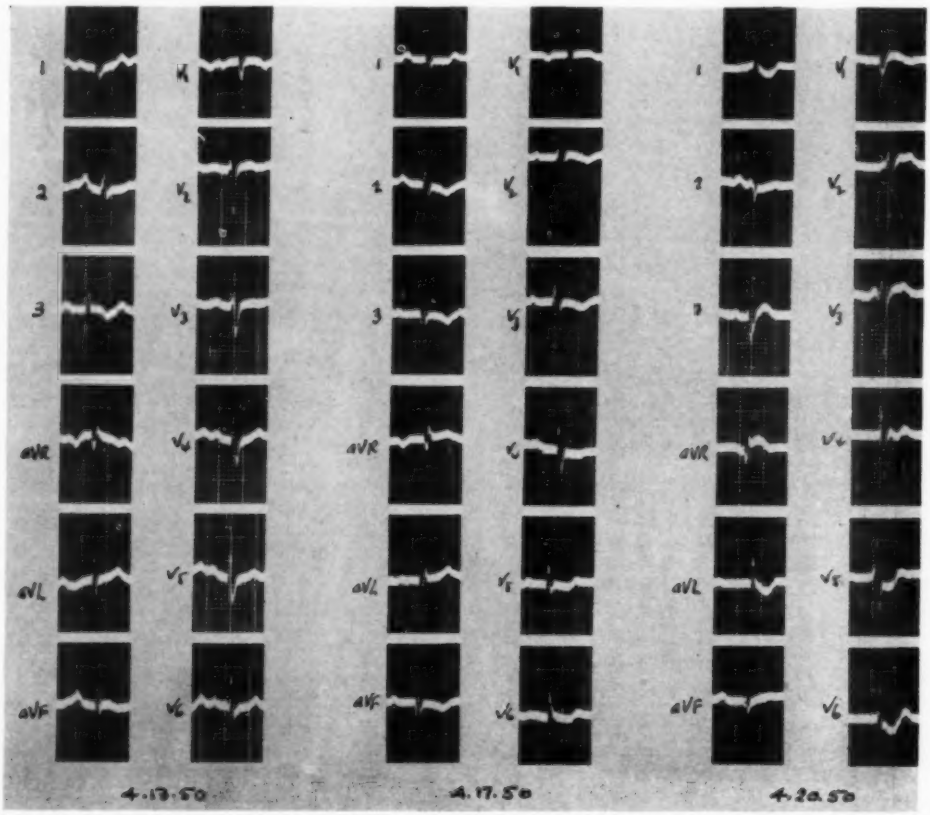

Fig. 2.—Serial electrocardiograms taken after a pulmonary infarction show (1) subsidence of the initial abnormalities with clinical improvement and (2) a recurrence following a second major attack. The record of April 13, 1950, shows the heart in a semivertical position with the transitional zone at V_6; a prominent R in aV_R and minor depression of S-T segments in I and V_6, a deep Q_3 and small Q_{AVF} are present. The record of April 17, 1950 reveals the heart in a more horizontal position, inversion of $T_{V2,3}$, and isoelectric S-T segments in $V_{5,6}$. The record of April 20, 1950, shows a shift of the transitional zone to the left, depression of S-T segments in I and $V_{5,6}$, elevation of S-T_{AVR} segment, and upright $T_{V2,3}$. There is a superimposed digitalis effect.

Case 2.—F. McG., a 73-year-old woman, entered Doctors Hospital on April 11, 1950, for resection of the sigmoid colon for carcinoma three weeks following a preliminary cecostomy. Physical examination at this time showed no other abnormalities. On April 13, 1950, the patient became acutely dyspneic, cyanotic, and revealed signs of shock. The pulse rate rose from 84 to 146 beats per minute, while the blood pressure fell from 140/82 to 60/40 mm. Hg. A roentgenogram of the chest revealed a wedge-shaped density in the lower portion of the right lung. Later, physical signs in the lower lobe of the right lung, dullness with increased breath sounds, bronchial breathing, and a pleural friction rub, accompanied by painful respirations and hemoptysis, became evident.

There was a definite improvement in the general status of the patient, as well as in the local signs, by April 17; by April 20, the condition was as noted at entry into the hospital. The condition remained the same until May 2, when a repetition of the shocklike syndrome occurred; she died within six hours. Post-mortem examination revealed carcinoma of the sigmoid colon extending into the adjacent lymph nodes, thrombosis of the iliac veins, and massive bilateral pulmonary infarction associated with obstruction of the major right and left pulmonary arteries. The coronary arteries were patent but showed moderate atherosclerosis. There was no evidence of myocardial infarction or coronary artery occlusion.

Comment.—The serial electrocardiograms on this patient (Fig. 2) illustrate the rapidity of development of abnormalities associated with pulmonary infarction. Subsidence of the rotational changes occurred with persisting evidence of right ventricular strain at the time of significant clinical improvement. The subsequent superimposition of myocardial anoxia and the shift of the transitional zone to the left followed a second pulmonary infarction that was not otherwise clinically demonstrable. Death occurred after a third infarction twelve days later.

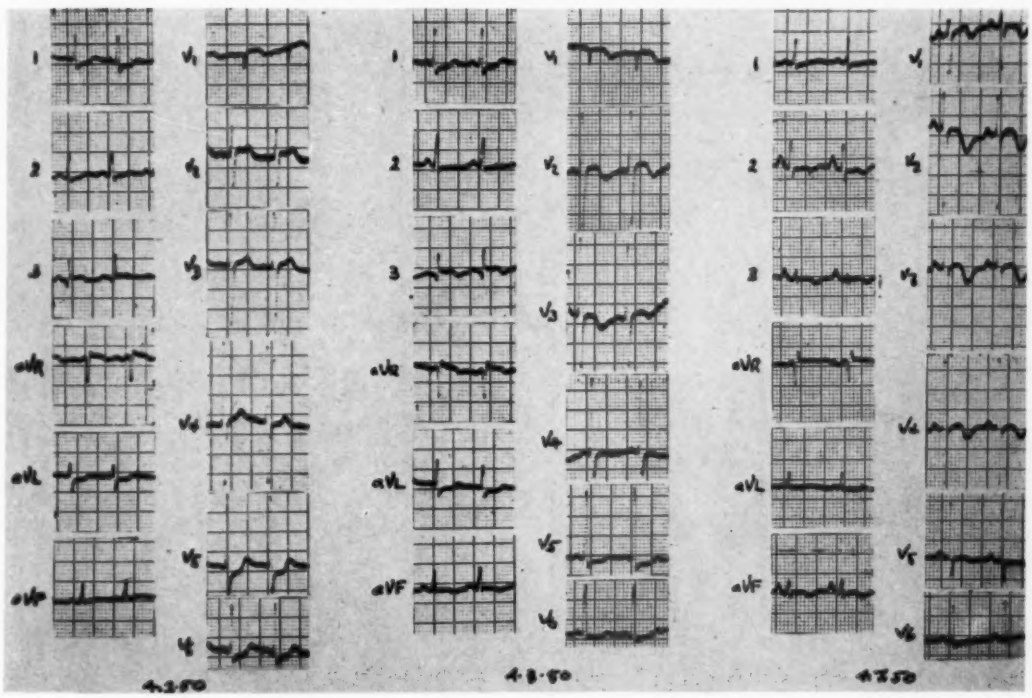

Fig. 3.—Serial electrocardiograms taken one hour after an acute pulmonary infarction show subsidence of the initial changes due to shift of the heart to a vertical position with clockwise rotation, despite persistence of right ventricular dilatation. The record of April 2, 1950, shows the heart in a semivertical position, deep Q_3, transitional zone at V_6, and depression of S-T segments in I and $V_{5,6}$. T_{V1-6} are upright. The record of April 3, 1950, shows additional inversion of T_{V1-2}, rising S-T segments in $V_{5,6}$ toward the base line, and reduction of the depth of S_{AVL}. The record of April 7, 1950, shows increasing depth of inversion of T_{V1-3}, isoelectric S-T segments in $V_{5,6}$, and the appearance of tall, peaked P waves in II, III, and aV_F.

CASE 3.—H. H., a 72-year-old woman, entered the San Francisco Hospital on April 1, 1950, following an automobile accident that resulted in multiple fractures, including a fracture of the

neck of the right femur. The blood pressure at entry was 90/60 mm. Hg. There was no evidence of shock, increased venous pressure, or congestive failure. The following day, the patient developed acute dyspnea and cyanosis. The blood pressure fell to a level which could not be measured, although there was a definite increase in venous pressure. These signs persisted for twenty-four hours and were followed by a rise in temperature and an increase of white blood cells to 21,000 per cubic millimeter. During the next five days the patient suffered from cough and hemoptysis; an x-ray examination at this time showed signs of pulmonary infarction. At the end of the five-day period, there was considerable clinical improvement. Successful nailing of the femoral fracture was then performed without further complications. A follow-up electrocardiogram taken two weeks later was normal.

Comment.—Serial electrocardiograms taken on this patient (Fig. 3) demonstrate the rapid onset of rotational and ischemic changes associated with pulmonary infarction and the delayed sequential development of right ventricular strain and right auricular dilatation. The reversibility of these changes was indicated by the appearance of a normal pattern two weeks after the third tracing.

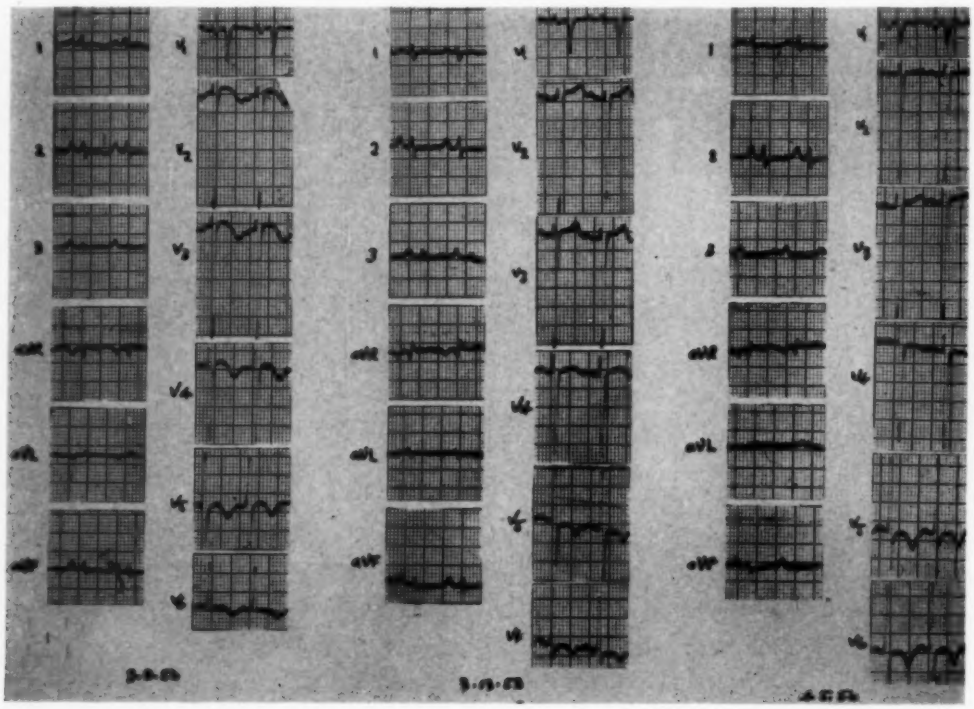

Fig. 4.—The record of March 8, 1950, shows the presence of tall P waves, small R_{AVR}, transitional zone at V_6, and deep inversion of T waves in $V_{2\text{-}6}$ which occurred several days after an extensive pulmonary infarction. The record of March 13, 1950, shows progressive changes, with increase in the height of R_{AVR}, shift of the transitional zone beyond V_6, and depression of S-T segments in $V_{5,6}$. The T waves in $V_{1\text{-}3}$ are upright. Although clinical improvement was evident at the time of the record of April 5, 1950, the P waves are more prominent. The transitional zone is beyond V_6, and $T_{V5,6}$ remains sharply inverted.

CASE 4.—A. T., a 46-year-old man, entered the hospital on March 6, 1950, with severe congestive failure, following an acute respiratory infection one month previously. Physical examination revealed anasarca. Gallop rhythm and an unusually accentuated second pulmonic heart sound were noted. The blood pressure was 90/62 mm. Hg. The liver was enlarged and was not tender. An x-ray film of the chest showed no abnormalities. On March 29, the patient developed a sudden, severe pain in the lower portion of the right side of the chest, pleural friction rub in this

area, evidence of increased venous pressure, and fever. X-ray examination of the chest showed a triangular density in the lower lobe of the right lung which was interpreted as a recent pulmonary infarction. After April 3, gradual progressive improvement was noted; the pulmonary signs abated, the gallop rhythm disappeared, the venous pressure decreased, and the patient's clinical condition reverted to the preinfarction status.

Comment.—Serial electrocardiograms (Fig. 4) taken after the occurrence of a major pulmonary infarction and during clinical improvement showed persistent evidence of auricular dilatation, clockwise rotation of the heart, posterior apical displacement, and right ventricular strain. These changes suggested either repeated minor pulmonary infarctions or the development of subacute changes possibly leading to a subsequent chronic cor pulmonale.

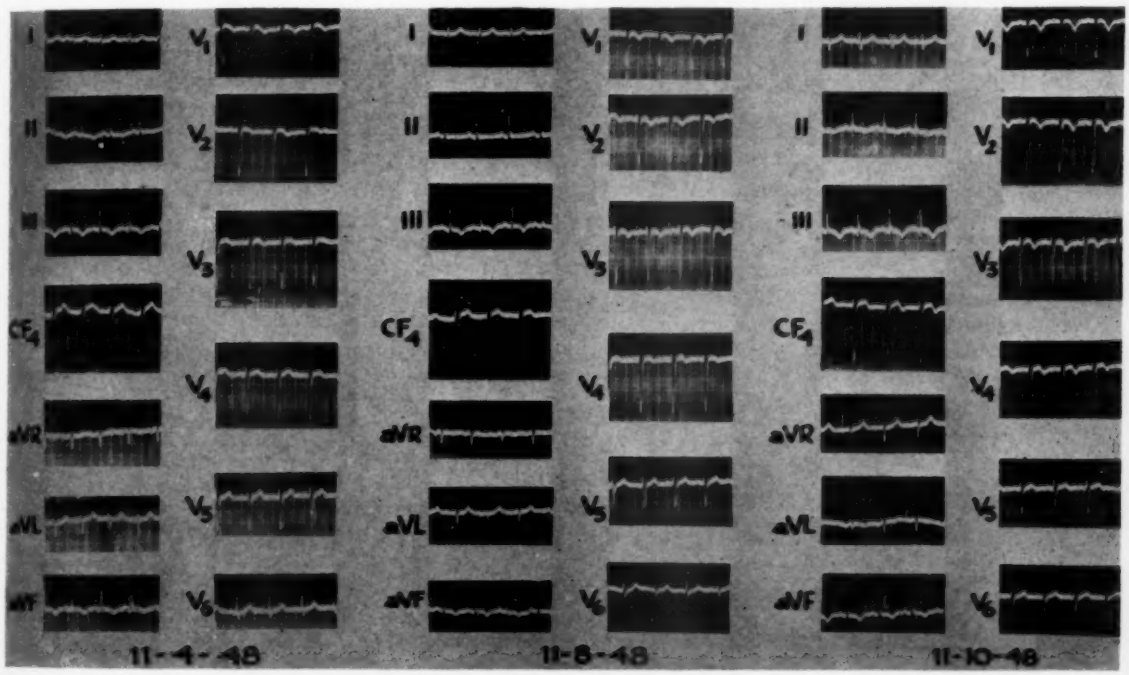

Fig. 5.—The record of Nov. 4, 1948 shows the heart in vertical position, with prominent Q_3, transitional zone at V_6, and inversion of T in II, III, aV_F, and $V_{1,2}$. CF_4 is not abnormal. In the record of Nov. 8, 1948, a small Q_{AVF} is present, T_{V1-4} is inverted, T_2 is isoelectric, and the transitional zone has shifted slightly to the left. The record of Nov. 10, 1948, reveals increase in the shift of the transitional zone to the left and increased inversion of T_{V1-4} and T_{CF4}; T_2 is again inverted.

CASE 5.—W. DeM., a 24-year-old man, was admitted to the hospital on Nov. 3, 1948, with complaints of dyspnea, weakness, and palpitation of three weeks' duration. These symptoms had occurred after an attack of severe pain in the lower left portion of the chest, accompanied by painful respirations and cough but without hemoptysis. Electrocardiograms taken prior to admission were stated to have been normal. Physical examination at entry revealed no signs of cardiac failure. The blood pressure was 100/80 mm. Hg. Fluoroscopic examination of the chest showed a questionable density in the upper lobe of the right lung and enlarged, vigorously pulsating pulmonary arteries. On November 5, a pleural friction rub became audible, and for the following six days clinical improvement was evident. On November 12, one hour after an examination that showed symptomatic and objective signs of further improvement, the patient was found dead. Post-mortem examination showed numerous, small, bilateral pulmonary infarcts of

varying duration, in addition to an acute, extensive embolism of the primary pulmonary artery. There were thromboses of the iliac veins. The right ventricle was considerably dilated but not hypertrophied, and the coronary arteries were normal. There was no evidence of myocardial infarction or coronary artery occlusion.

Comment.—Serial electrocardiograms (Fig. 5) in repeated pulmonary infarction in a young adult showed the heart in a vertical position with progressive changes due to clockwise rotation. Evidence of right ventricular strain and the occurrence of a small Q wave in aV_F and inversion of $T_{CF\,4}$ were noted. No electrocardiographic evidence of coronary insufficiency was observed. Post-mortem examination showed normal coronary arteries and no evidence of myocardial infarction.

CASE 6.—B. D., a 90-year-old woman, was brought into the hospital in an unconscious state on July 8, 1950. No antecedent history was available. Physical examination revealed an aged woman with a moderate degree of fever and periodic breathing. There was a flaccid hemiplegia of the left side. The heart appeared normal except for auricular fibrillation. Examination of the spinal fluid was negative. A blood count showed 12,800 white blood cells per cubic millimeter with 88 per cent polymorphonuclear neutrophils. An electrocardiogram revealed left ventricular hypertrophy. On July 10, the patient regained consciousness, although the hemiplegia persisted. Within several days severe congestive failure developed, and signs of consolidation of the lower lobe of the right lung became evident. On July 21, at the time of the second electrocardiogram, the pulmonary signs were well defined. The patient died twenty-four hours later. Post-mortem examination revealed massive infarction of the right lung caused by pulmonary artery occlusion, arising from extensive thrombi of the right ovarian veins. The heart showed no auricular or mural thrombi, and the coronary arteries were patent. There was no evidence of myocardial infarction.

Comment.—The electrocardiograms on this patient (Fig. 6) demonstrate the occurrence of auricular fibrillation, clockwise rotation of a horizontal heart, and changes resulting from right ventricular strain, manifested by inversion of $T_{V\,1\text{-}2,\,3}$ and subendocardial ischemia. These were early phenomena, produced by an acute fatal pulmonary infarction. Post-mortem examination showed the heart to be normal in all other respects.

CASE 7.—F. V., a 73-year-old man, entered the hospital on June 27, 1950, with a history of an acutely strangulated right inguinal hernia of twenty-four hours' duration. Previously, he had been treated for arteriosclerotic heart disease with congestive failure. Physical examination, showed no abnormalities, except for a blood pressure of 162/82 mm. Hg and the hernial lesion. Operative repair of the hernia without bowel resection was performed the same day. The postoperative course was uncomplicated until July 3, when the patient became acutely dyspneic, cyanotic, and developed an increase in venous pressure to 22 cm. of water. The next day, clinical and radiographic evidence of a pulmonary infarction in the lower lobe of the right lung was found. An increased excretion of urobilinogen in the urine also was noted. The dyspnea and other signs persisted, and the patient died on July 9, 1950.

An electrocardiogram on July 3, taken within one hour of the onset of a major postoperative pulmonary infarction, showed the presence of right bundle branch block and multiple ventricular premature beats arising from several foci. An electrocardiogram taken the following day revealed the heart in a horizontal position and disappearance of the bundle branch block. The transitional zone was to the left of V_6 with depression of ST segments in $V_{2\text{-}6}$.

Comment.—Serial electrocardiograms on this patient showed a transient right bundle branch block in a heart in a horizontal position which occurred immediately after the development of a pulmonary embolism. Despite progressive circulatory failure, normal ventricular conduction was resumed twenty-four hours later. Just prior to death, an increase in the clockwise rotation of the heart and subendocardial ischemia occurred.

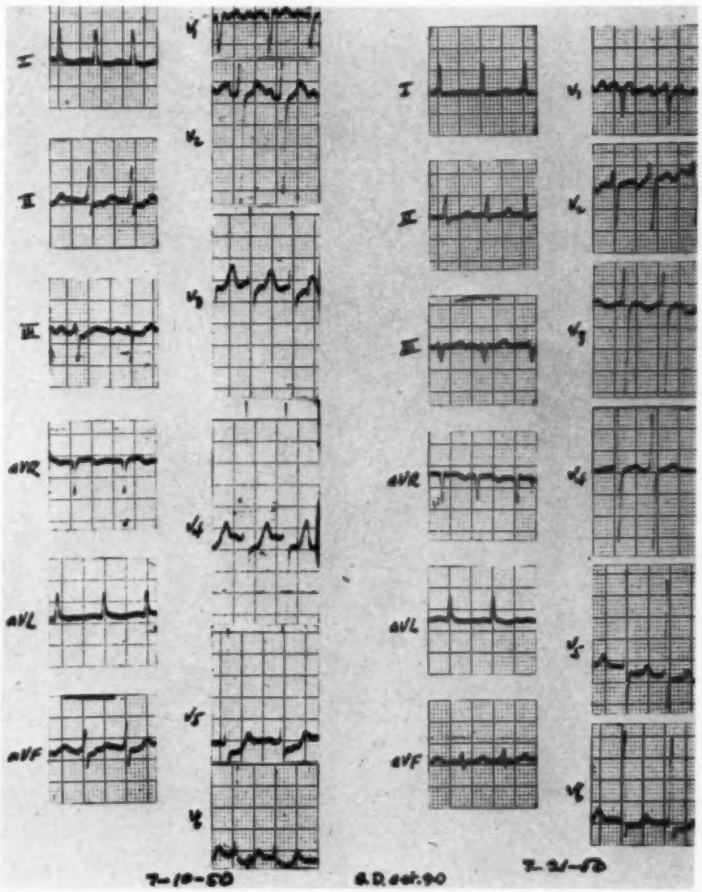

Fig. 6.—The record of July 10, 1950, reveals the heart in a semihorizontal position, with auricular fibrillation, transitional zone at V_5, and depression of S-T segments in V_{3-6}. The record of July 21, 1950, shows the persistence of the arrhythmia, slight shift of the transitional zone to the left, with a reduction in the depression of S-T segments in V_{3-6} and the development of inverted T waves in V_{1-3}.

CASE 8.—S. L., a 72-year-old woman, entered the San Francisco Hospital on Nov. 29, 1949. Two days previously she had noted a sudden sharp pain in the lower thoracic region. Since that time, she had experienced some pain on breathing, but had no cough, hemoptysis, dyspnea, or fever. Physical examination revealed no abnormalities in the lungs. The pulse was regular at the rate of 96 per minute; the blood pressure was 140/92 mm. Hg. A Grade 2 systolic murmur was heard over the apex of the heart. There was no evidence of peripheral venous disease. X-ray examination of the chest at this time showed no abnormalities. On December 5, the patient suddenly became extremely cyanotic and dyspneic and developed signs of shock. The blood pressure fell to 80/60 mm. Hg. Death occurred ten hours later. Clinical diagnosis of pulmonary infarction seemed justified, although it could not be substantiated by other means.

Comment.—The serial electrocardiograms taken on this patient (Fig. 7) illustrate the electrocardiographic changes that follow a major pulmonary embolism. There was a shift of the electrical position of the heart toward the vertical, with anterior displacement of the apex and marked clockwise rotation, and superimposed myocardial anoxia, causing the "staircase" effect. These changes occurred within five hours of the attack.

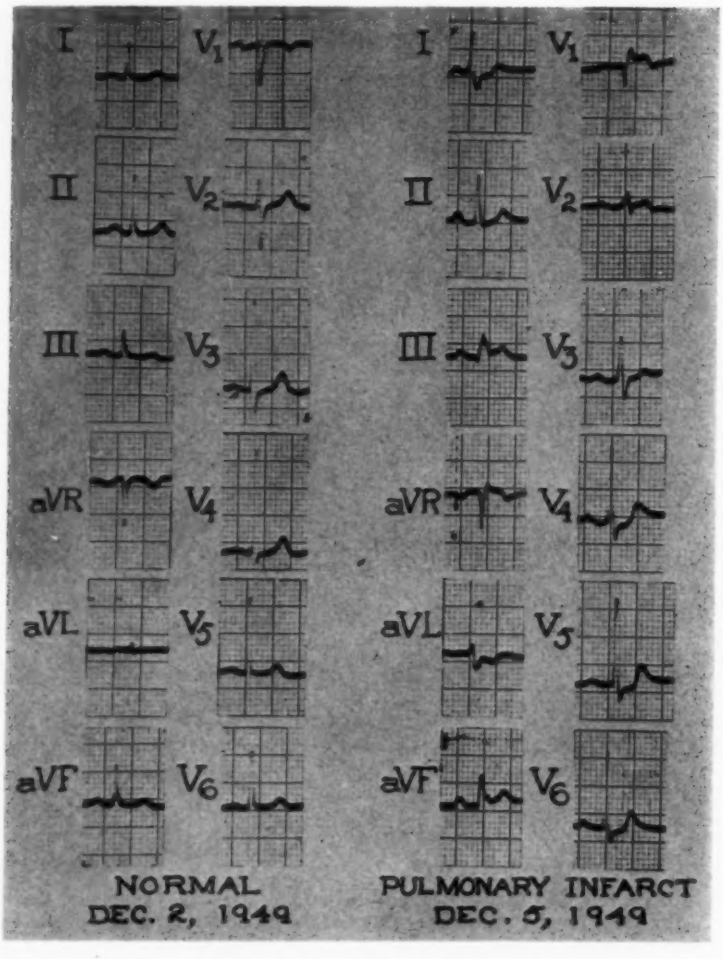

Fig. 7.—Electrocardiograms taken before and after the occurrence of a massive pulmonary embolism that terminated in death five hours after the second record. Record of Dec. 2, 1949, shows the heart in a semivertical position, downward major deflection in aV_R, and the transitional zone at V_3. Record of Dec. 5, 1949, reveals an increase in the vertical position of the heart, prominent R_{AVR} and R_{V1}, depression of S-T segment in I, aV_L, and V_{4-6}, with shift of the transitional zone toward the left.

DISCUSSION

In acute cor pulmonale the occurrence of anatomic rotational changes in the position of the heart can be detected by abnormalities in the electrocardiogram.[11,12]

The production of dilatation of the right ventricle as a basic cardiac phenomenon in pulmonary embolism has been demonstrated experimentally in animals and correlated with the clinical syndrome.[13] The speed with which the associated electrocardiographic changes appear is a diagnostic feature that frequently aids in differentiating acute cor pulmonale from myocardial infarction.[14] The early phase of myocardial infarction is rarely associated with alteration in the position of the heart. Later in the course of the disease, when there is no problem of diagnosis, rotation may occur with such complications as perforation of the interventricular septum or the development of a ventricular aneurysm.[15]

In the present study, the shift of the transitional zone to the left in serial electrocardiograms was the most frequent evidence of acute cor pulmonale. The shift was especially well defined in those instances where a control record had been taken before the attack occurred. In two cases, the fact that the heart resumed a more normal position at the time of resolution of the pulmonary infarction was an important corroboratory sign. The occurrence of rotation of the heart to the vertical position in conjunction with the clockwise rotation was also of considerable importance. The degree of rotation on the anteroposterior axis was significantly less in patients with left ventricular hypertrophy, possibly because of the inertia of the muscle mass. The manifestations of actual right ventricular strain, presumably resulting from increased pulmonary arterial pressure, occurred most frequently in the initial phase of the condition, and in some cases showed the reversibility that characterized the rotational phenomena. It is apparent that the association of right ventricular strain and clockwise rotation accounts for the T-wave inversion in CF_2 and/or CF_4 that was empirically described several years ago. The occurrence of transient, reversible right bundle branch block in acute pulmonary arterial obstruction as an early sign suggests a causal relationship to right ventricular strain.

The occurrence of increased peripheral pulmonary resistance that was of sufficient degree to cause right auricular dilatation (P-pulmonale) was consistently delayed, was usually preceded by electrocardiographic evidence of right ventricular strain, and was of grave prognostic significance.

Coronary insufficiency occurred primarily in hearts previously damaged either by the ventricular hypertrophy of prolonged arterial hypertension or by coronary artery sclerosis. These patterns of myocardial anoxia, with depression of S-T segments in precordial leads derived from the left ventricle, added to the effects of vertical and clockwise rotation of the heart, can readily be seen to account for the "staircase" ascent of standard Leads I and II.

In none of the patients in the present series was the presence of posterior myocardial infarction a confusing factor. A prominent Q wave in Lead III was observed in the electrocardiograms in four of the patients in the series. It was associated with a definite Q_{AVF} in three instances, and clockwise and vertical rotation was present in all three. The occurrence of a significant degree of vertical rotation of the heart and leftward shift of the transitional zone was found to be presumptive evidence of an acute cor pulmonale, whether or not a distinct Q wave was detected in Leads III and/or aV_F.

SUMMARY AND CONCLUSIONS

1. A group of eight patients with acute cor pulmonale caused by pulmonary infarction or massive pulmonary embolism and verified by clinical signs, roentgenographic evidence, or post-mortem examination was studied by means of serial electrocardiograms.

2. Augmented extremity lead and unipolar precordial lead records showed shift of the interventricular transitional zone to the left (clockwise rotation of the heart) in all eight patients; in seven of these the shift was detectable early in the course of the disease.

3. Increase in the vertical position of the heart was found in six patients and evidence of right ventricular dilatation in four.

4. Evidence of coronary insufficiency was found in four patients. It was consistently associated with pre-existent coronary artery disease and occurred uniformly in the older age group.

5. Auricular arrhythmias were detected in three patients. In all instances they occurred many hours after the initial infarction or embolism. Right auricular dilatation was present in two patients and was also a delayed phenomenon.

6. Transient right bundle branch block was noted in one patient as an early electrocardiographic change.

7. Review of the records obtained revealed that the so-called "staircase" ascent of the S-T segment in standard Lead I, previously described in acute cor pulmonale, is produced when an increase in the vertical position of the heart with clockwise rotation is superimposed upon changes associated with coronary insufficiency.

8. Inversion of T waves in Leads CF_2 and/or CF_4 is apparently caused by clockwise rotation of the heart, usually in conjunction with evidence of right ventricular strain.

9. The presence of a Q wave in Leads III and/or aV_F occurred as a manifestation of the rotational changes in acute cor pulmonale in the absence of posterior myocardial infarction.

10. The rapidity of the electrocardiographic changes is important in differentiating acute cor pulmonale from myocardial infarction.

11. The electrocardiographic patterns produced by rotational changes are more consistent than any other evidence in acute cor pulmonale. If serial records are obtained at the onset, even minor degrees of shift of the transitional zone can be shown to be of diagnostic significance.

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THE PROGNOSTIC SIGNIFICANCE OF THE ANOXEMIA TEST IN CORONARY HEART DISEASE

A Follow-Up Study of 254 Subjects

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As an aid in the detection of coronary insufficiency, the clinical value of the anoxemia test, described in 1939,[1] has been confirmed by numerous reports of its successful use both in this country and abroad. The most recent publication is that of Nylin, of Stockholm, who has analyzed the results of 1,130 tests performed in his clinic.[2] If the prescribed precautions are observed, no hazard is involved.[3] A large experience has demonstrated that the criteria of a positive result, as outlined, are valid.[4] Observations made with unipolar extremity leads have not contributed significantly to the evaluation of a positive or a negative test[5]; nor is the level of hypoxemia induced the critical determining factor in the production of a positive reaction.[5,6] Three points merit emphasis: (1) The test should be employed clinically only when the diagnosis is in doubt; hence, its use is restricted to a relatively small, but important, group of cases. (2) A positive result, in our experience, affords objective evidence of coronary insufficiency. (3) A negative result does not rule out the possible presence of coronary heart disease. A test which is electrocardiographically negative but during which pain is produced similar to that felt during spontaneous anginal attacks is regarded as *presumptively* positive.[4] The subsequent history of a considerable number of patients in whom this type of reaction occurred justifies this conclusion.

The question naturally presents itself as to whether the outcome of the test, be it positive or negative, carries with it any prognostic significance. This study was designed to furnish an answer; in reviewing the assembled information, certain features pertaining to the clinical course of coronary disease have become apparent.

MATERIAL AND METHODS OF ANALYSIS

The clinical material is composed of subjects who were given the anoxemia test in our laboratory during the ten-year period 1937 to 1947. Only those are included who are known to be dead or about whose later course reliable informa-

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tion could be obtained at least one year after the initial test. Such information was found in the records of the Presbyterian Hospital or of other institutions in which the patients were treated or died. In some instances the fact or cause of death was furnished by relatives. In order to trace as many as possible, a search was made of the death certificates filed in the Bureau of Records and Statistics of the Department of Health of the City of New York.* In view of the thoroughness of this search and because practically all of the subjects were residents of New York City, it seemed reasonable to assume that any of these persons not known to be dead were alive in 1947 at the time the study was terminated. Since some of the subjects might have died elsewhere than in the city, the mortality rates calculated for the various groups may be somewhat too low.

The series consisted of 254 individuals (Table I). Of these, 103 were persons with no evidence of cardiovascular disease, ranging in age from 24 to 74, with an average of 47 years. There were 100 patients with coronary heart disease who experienced anginal attacks; these ranged in age from 34 to 75, with an average of 55 years. In twelve individuals, the presence of coronary sclerosis with anginal pain was suspected but was in doubt, both before and after the test. There were twenty-nine patients with manifest coronary disease without anginal pain. In ten patients the diagnosis was essential hypertension.

TABLE I. CLINICAL MATERIAL AND DURATION OF FOLLOW-UP

CLINICAL DIAGNOSIS	SUBJECTS			AGE (YEARS)		DURATION OF FOLLOW-UP (YEARS)	
	TOTAL	LIVING	DEAD	AVERAGE	RANGE	AVERAGE	RANGE
No cardiovascular disease	103	94	9	46.8	24–74	6.6	1–10
Coronary sclerosis with pain	100	57	43	55.1	34–75	5.9	<1–10
Suspected coronary sclerosis with pain	12	12	0	53.5	39–68	6.2	2– 9
Coronary sclerosis without pain	29	21	8	58.0	40–77	5.4	1– 9
Hypertension	10	7	3	50.0	40–67	5.5	3– 9
Totals	254	191	63	51.8	24–77	6.1	<1–10

Most of the living were retested and re-examined at least once. In many cases the anoxemia test was repeated on numerous occasions, and frequent visits to the outpatient department were made. The duration of the follow-up period of the various subjects ranged from less than one year to ten years and was 6.1 years for the total group.

Of the 254 individuals, sixty-three are known to have died during the follow-up period; in the sixteen on whom an autopsy was performed, the clinical diagnosis was confirmed in every instance. In the group with coronary sclerosis

*The staff of the Bureau rendered helpful assistance.

and anginal pain, forty-three patients died, and ten autopsies were done. Of these forty-three, twenty-two died following an acute myocardial infarction, nine died suddenly, presumably of acute coronary insufficiency, and six succumbed to congestive heart failure. The remaining six died of noncardiac causes.

TABLE II. DURATION OF SYMPTOMS PRIOR TO INITIAL TEST IN PATIENTS WITH CORONARY SCLEROSIS

RESULT OF TEST	DURATION OF SYMPTOMS (YEARS)	
	AVERAGE	RANGE
Negative	3.0	1–9
Positive	3.7	0.5–14
Negative with pain	4.6	0.5–16
Total group	3.7	0.5–16

TABLE III. CLINICAL STATUS OF 58 PATIENTS WITH CORONARY SCLEROSIS AND ANGINAL PAIN 2 TO 10 YEARS AFTER INITIAL TEST

RESULT OF INITIAL TEST	LATER CLINICAL STATUS			
	BETTER	WORSE	UNCHANGED	TOTAL
Negative	4	2	8	14
Positive	14	6	9	29
Negative with pain	3	8	4	15
Totals	21	16	21	58

TABLE IV. RESULT OF RETEST 2 TO 10 YEARS AFTER INITIAL TEST IN 40 PATIENTS WITH CORONARY SCLEROSIS AND ANGINAL PAIN

RESULT OF INITIAL TEST	RESULT OF RETEST			
	NEGATIVE	POSITIVE	NEGATIVE WITH PAIN	TOTAL
Negative	3	6	5	14
Positive	3	10	3	16
Negative with pain	3	5	2	10
Totals	9	21	10	40

RESULTS

Statistical methods have been employed in an attempt to find correlations between the result of the anoxemia test, the clinical status, and the prognosis.*

*Dr. John W. Fertig, Professor of Biostatistics in the School of Public Health of the Faculty of Medicine of Columbia University, aided in making the statistical analyses.

The outcome of the tests was studied in relation to various factors, such as age, sex, previous or subsequent myocardial infarction, presence or absence of hypertension, normal or abnormal control electrocardiogram, and the presence or absence of cardiac enlargement. The results of these analyses have been inconclusive due, in most instances, to the small numbers involved. Only the tables relating to the more pertinent factors are presented.

In the group with coronary sclerosis and anginal pain, no correlation could be shown between the result of the test and the age of the subject or the duration of symptoms prior to the initial test (Table II). It is clear also that, for those subjects still alive whose later clinical status could be determined, there is no demonstrable relationship between the result of the initial test and the condition of the patients two to ten years after this test was made (Table III). Likewise, the initial test furnishes no information as to the result of a retest two to ten years later, at least for those on whom a retest was made (Table IV).

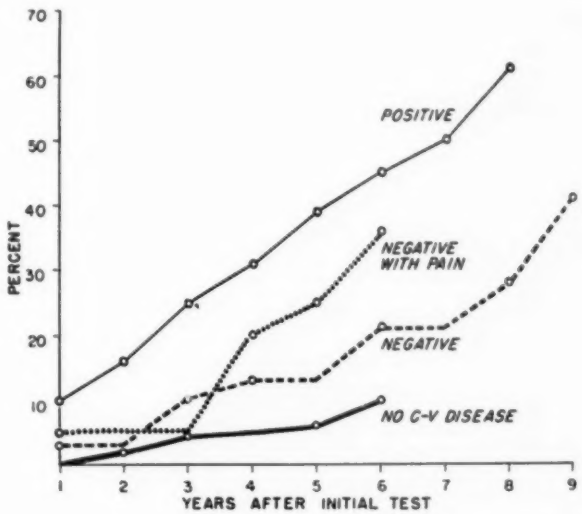

Fig. 1.—Cumulative mortality rates in 100 patients with coronary heart disease and anginal pain and in 103 individuals with no cardiovascular disease, grouped according to result of initial anoxemia test.

Comparison of the mortality rates, however, has yielded more definite information. In Fig. 1, these are charted for 100 patients with coronary disease and anginal pain and for 103 individuals with no evidence of a cardiovascular disorder, grouped according to the result of the initial anoxemia test. The cumulative percentage of those dying in any specified period after the original test was performed was computed by an actuarial procedure. The eight-year mortality rate for the coronary group with a positive test was 61 per cent; for the group with a negative test it was 28 per cent. This is a statistically significant difference. The six-year mortality rate for the patients with a positive test was 45 per cent; for those with a negative electrocardiographic result who experienced pain during the test (presumptively positive), it was 36 per cent, and for those with a

negative result without pain, it was 21 per cent. The mortality rate for the individuals with no cardiovascular disease during the same period was 10 per cent. The only significant difference in the six-year mortality rates is that between the patients with a positive result and the subjects with no cardiovascular disease. The difference between those with a positive result and those with a negative result is only of borderline significance. The patients who experienced pain during the test but developed no changes in the form of the electrocardiogram (presumptively positive reaction) showed a mortality rate intermediate between those with positive and negative tests. It seems probable that, had the series been larger, the differences between these three groups would have been accentuated.

COMMENT

Very little information is available concerning the usefulness of the anoxemia test in prognosis. Burchell, Pruitt, and Barnes concluded that patients with coronary sclerosis and a positive reaction have as good an outlook as those with a negative test.[5] Their information was based on answers to questionnaires returned by 204 patients on whom the test had been done at the Mayo Clinic during the first three years it was used, with follow-up periods of three to six years. The series reported by Biörck and Dalhamn[7] comprised 243 cases studied between the years 1942 and 1946. The average follow-up period was about seven years. The mortality rate was higher for those with a positive reaction than for those in whom it was negative. In the group with positive tests the average life expectancy was shorter in men than in women; however, the average age of women was lower when the test was made. Negative tests were followed by cardiac death in less than six months in five patients, lending support to the statement that a negative reaction does not exclude advanced heart disease.

Our own findings appear to show that a positive reaction indicates not only the presence of coronary insufficiency at the time of the test, but also a poorer ultimate prognosis with respect to longevity. This conclusion is particularly applicable to the patients who are subject to attacks of anginal pain. It should be borne in mind that, whereas this is true for the group as a whole, it does not necessarily apply to the individual patient. Atherosclerosis is inherently a progressive disease. Its effects on the effective functioning of the coronary circulation depend upon the balance established between impairment caused by the pathologic process and improvement following development of collateral channels. That these changes may take place without symptoms has been shown by the clinical and pathologic studies of Blumgart and associates[8] and by the serial electrocardiographic observations reported from our laboratory.[9] The more marked the encroachment on the coronary reserve, the greater is the stimulus for the formation of new vascular channels. Barring an acute accident which may cause sudden imbalance, such as the occurrence of thrombotic occlusion, the clinical course will vary according to whether damage or repair is the preponderant factor.

In view of the dynamic nature of the processes induced by atherosclerosis, it is obvious that any functional test of the coronary circulation can reflect only the condition at the time of its performance. To be sure, a positive test indicates significant reduction of the coronary reserve and appears to foretell a relatively graver future, but the course is influenced by many variables, most of which, at present, are beyond human control. On the basis of our limited data, apparently it is impossible to foretell the result of a retest or what the clinical status will be at any time. Our observations add confirmation to the impression that, within wide limits of probability, the fate of the patient with coronary heart disease is unpredictable.

SUMMARY

1. In order to appraise the prognostic value of the anoxemia test, a follow-up study was made of 254 individuals on whom it was performed during the decade 1937 to 1947. Included were 141 patients with manifest or suspected coronary heart disease, ten with hypertension, and 103 with no evidence of a cardiovascular disorder. The average follow-up period was six years.

2. Sixty-three individuals died during the course of the study. In the sixteen cases in which an autopsy was performed, the clinical diagnosis was confirmed.

3. The material was analyzed by statistical methods in an effort to find correlations between the result of the anoxemia test, the clinical status, and the prognosis. The results were inconclusive.

4. A comparison of the cumulative mortality rates of the patients with coronary sclerosis and anginal pain and the noncardiac subjects, grouped according to the result of the initial anoxemia test, showed distinct differences. In the coronary patients whose tests were positive, the prognosis was significantly worse, with respect to longevity, than in those whose tests were negative. It should be emphasized, however, that, whereas this obtains for the group as a whole, it does not necessarily apply to any individual patient.

5. The anoxemia test furnishes an index of the coronary reserve only at the time of its performance. Because of the numerous uncontrollable variables affecting the lesions of atherosclerosis, it is not possible to predict accurately, within a wide range of probability, the future clinical course of the patient with coronary heart disease.

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THE IMPORTANCE OF PATENT DUCTUS ARTERIOSUS IN INFANTS

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IT IS generally stated that the optimum time for surgery of patent ductus arteriosus is in the age range of from 5 to 12 years. It is not only implied but definitely stated that below the age of 3 to 5 years the diagnosis cannot be made with certainty and that if it were made during infancy, operation should probably be postponed anyway.[23,30] To clarify the point of view that an accurate diagnosis can be made in infancy and to emphasize the fact that surgical intervention in uncomplicated patent ductus arteriosus in infants is not infrequently a lifesaving procedure, the appropriate literature has been reviewed and a series of twenty-two additional cases analyzed.

REVIEW OF THE LITERATURE

Despite opinions to the contrary,[7] an uncomplicated patent ductus arteriosus may be a clinically important defect during infancy. Thus, Abbott[1] reported twenty deaths during infancy in a group of ninety-two patients with patent ductus arteriosus, an incidence of approximately 25 per cent. Similarly, Wilson and Lubschez,[31] on the basis of sixty-three cases of patent ductus arteriosus (in a series of 54,842 collected autopsy cases) reported: "In the majority of cases with this defect death occurred in infancy or early childhood." In their own series of sixteen patients with autopsies fourteen died before reaching 1 year of age. Other cases have been reported in which an otherwise uncomplicated patent ductus arteriosus has resulted in cardiac enlargement, congestive heart failure, or death during infancy.[8,19,20,21] Furthermore, the fatal complications of aseptic thrombosis with systemic embolization and necrosis[18] and aneurysm of the ductus with rupture[22] have been reported in this age group. The most recent publication is that of Keith and Forsyth[21] in which six infants were reported to have cardiac enlargement or congestive failure in the proved presence of an uncomplicated patent ductus arteriosus. To these reports may be added the following twenty-two patients, eight of whom were 1 year of age or younger.

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TABLE I. CLINICAL AND LABORATORY DATA IN TWENTY-TWO IN

NO.	NAME	SEX	AGE	CLINICAL DATA								ROENTGENOGRAM					
				CONGESTIVE FAILURE	GROWTH IMPAIRMENT	SUBACUTE BACTERIAL ENDOCARDITIS	CYANOSIS	BASAL MURMUR	APICAL MID-DIASTOLIC MURMUR	ACCENTUATION OR REDUPLICATION OF P_2	BLOOD PRESSURE (MM. Hg)	CARDIOTHORACIC RATIO	LV	RV	LA	RA	PULMONARY VASCULATURE
1	R. L. preop.	M	6 wk.	−	+	−	−	C	−	+	−	61.3	−	(AP)	−	−	−
	R. L. postop.		12 wk.		−			−	−	−	−						
2	J. M.	M	3 mo.	+	+	−	−	S*	−	+	90/60	64.5	+	−	+	−	+
3	K. Z.	F	3½ mo.	+	−	−	−	S*	+	+	80/50	57.5	+	−	+	−	+
4	S. S.	F	4 mo.	+	−	−	−	S	+	+	−	60.0	(LAO)	(AP)	+	−	+
5	S. J.	M	6 wk.	−	+	−	−	S	−	+	−	56.1	−	−	−	−	−
	S. J.		5 mo.	−	+	−	−	C	−	+	85/15						
6	C. M.	M	9 mo.	−	+	−	−	S+D	−	+	110/50	64.6	+	+	+	−	+
7	R. R.	M	1 yr.	−	+	−	−	C	−	+	80/10-0	66.0	+	−	−	+	−
8	L. S.	M	1 yr.	−	+	−	−	S	−	+	−	62.5	+	−	−	−	+
9	B. H.	F	1½ yr.	−	+	−	−	C	−	+	−		+	−	+	−	+
10	K. K.	M	1½ yr.	−	−	−	−	C	−	+	100/0	60.0	+	−	+	−	+
11	P. L.	F	1½ yr.	−	+	−	−	C	−	+	100/50	65.0	+	−	−	−	−
12	S. P.	M	2 yr.	−	−	−	−	C	−	+	130/45	56.2	+	−	−	−	−
13	L. N.	F	2 yr.	−	−	−	−	C	−	+	110/40	63.6	−	−	+	−	−
14	N. P.	F	2 yr.	−	+	−	−	C	−	+	100/10-0	54.0	+	−	−	−	−
15	W. J.	M	2½ yr.	−	−	−	−	C	−	+	100/45	60.0	+	−	+	−	+
16	M. L. B.	F	2½ yr.	−	−	−	−	C	−	+	95/40	57.8	+	−	−	−	−
17	N. M.	F	2½ yr.	−	−	−	−	C	−	+	120/70	56.2	+	−	+	−	+
18	R. R.	F	3 yr.	−	−	−	−	C	−	+	−						
19	S. S	F	3 yr.	−	−	−	−	C	−	+	100/60						
20	S. W.	F	3 yr.	−	−	−	−	S	+	+	80/60	58.2	+	−	−	−	+
21	S. L. F.	M	3 yr.	−	−	−	−	S+D	−	+	100/10	59.6	+	−	−	−	−
22	R. A. S.	F	3 yr.	−	−	−	−	C	−	+	100/40	56.0	−	−	−	−	−

Key to abbreviations: C = continuous
S = systolic
S* = systolic, continuous murmur with the catheter in the ductus
D = diastolic
RVH = right ventricular hypertrophy
LVH = left ventricular hypertrophy
Rt. BBB = right bundle branch block
N = normal

†The upper figure in each set of two represents mean pressure in centimeters of water; the lower figure in each set represents oxygen saturation in per cent.

Note: For discussion of important correlations see the text.

TWO INFANTS WITH PATENT DUCTUS ARTERIOSUS

ELECTROCARDIOGRAM						PHYSIOLOGICAL DATA†						ANATOMY	SURGICAL DATA
P	QRS	V_1	V_6	QRS AXIS		VC	RA	RV	PA	AO	PA PRESSURE = % AO		
080	065	036	032	−75	RVH	11.0	11.0	28.0	36.0	80.0	45.0		Operated successfully
					LVH	72.7	—	—	—	86.4			
					Rt. BBB	12.0	12.0	20.0	28.0				
						—	—	—	—				
074	06	020	040	±0	LVH	10.0	10.0	54.0	73.0	94.0	77.8		Operated successfully
						27.0	44.3	47.0	72.2	81.8			
074	06	014	024	+72	LVH	20.0	20.0	67.0	74.0	98.0	75.5		Operated successfully
						55.2	52.5	43.0	65.8	80.0			
080	06	010	026	+98	LVH								Died preoperatively
080	06	020	032	+45	N	16.0	16.0	32.0	57.0	111.0	51.3		Operated successfully
						67.7	67.5	66.8	81.2	90.7			
080	07	042	026	+90	Rt. BBB	16.0	16.0	52.0	68.5			Anomalous pulmonary venous return	Operated successfully
						65.3	69.6	68.2	85.8				
100	07	044	036	+90	Rt. BBB	12.5	12.5	26.0	33.0	76.0	43.5		Operated successfully
						56.7	60.0	54.5	73.4	99.0			
055	08	030	030	+78	Rt. BBB							Interventricular septal defect	Operated successfully
080	08	036	030	+57	Rt. BBB								Operated successfully
080	07	016	040	+76	LVH								Died during anesthesia
100	06	020	040	+75	LVH	11.0	11.0	35.0	52.0	119.0	43.7		Operated successfully
						65.3	63.4	65.3	81.5	92.5			
080	07	020	040	+46	LVH								Operated successfully
060	06	020	032	+77	N								Operated successfully
075	065	018	032	+90	N								Operated successfully
080	07	015	048	+42	LVH								Operated successfully
120	07	014	038	+75	LVH								Operated successfully
100	06	020	024	+80	N	14.0	14.0	42.0	44.0				Operated successfully
						70.8	67.5	70.8	81.3				
080	07	016	038	±0	LVH								Operated successfully
060	07	020	038	+17	LVH								Operated successfully
090	07	018	032	+120	Rt. BBB	12.0	13.0	50.0	86.0	106.5	81.2	Residual diastolic murmur	Operated successfully
						48.9	49.4	50.5	74.0	85.2			
090	08	016	040	+81	LVH			32.0	57.0	70.0	81.5		Operated successfully
							51.8	55.1	83.5	86.9			
080	07	020	034	+45	N								Operated successfully

CLINICAL OBSERVATIONS

A summary of the data in twenty-two patients from the age of 6 weeks to 3 years in whom a patent ductus arteriosus was the major or only cardiovascular defect is given in Table I. Without attempting to state all of the possible observations which could be made from these data, attention will be directed primarily toward those of greatest clinical importance. Furthermore, an attempt will be made to present the material listed according to group categories in a correlative fashion.

The most characteristic auscultatory finding of patent ductus arteriosus in older children is the continuous murmur as originally described by Gibson.[15] A number of current beliefs regarding this murmur require critical re-evaluation; among these are the following:

1. The usual time of appearance of the "typical" murmur is generally stated to be at the age of 3 to 5 years.
2. Below this age the continuous murmur is supposedly infrequent, and its presence justifies the suspicion of either the presence of a complicating defect, such as pulmonary stenosis or coarctation of the aorta, or an entirely different diagnosis than patent ductus arteriosus.
3. Surgical intervention is usually considered to be contraindicated in the absence of a continuous murmur.

It is also known from various reports that under certain circumstances, particularly with a large ductus and marked pulmonary hypertension, there may be only a systolic murmur or occasionally even no murmur at all.

The following observations were made from the present study:

1. Except in the presence of a complicating pulmonary hypertension, a typical continuous murmur was invariably present by the age of 18 months.
2. A continuous murmur may be and frequently was present in infants with an uncomplicated patent ductus arteriosus, as illustrated by two patients aged 6 weeks and 5 months, respectively.
3. All the infants had at least a systolic murmur which occurred alone more commonly than with a diastolic component under the age of 1 year.

The presence or absence of a diastolic component to the murmur of patent ductus arteriosus at any age apparently depends upon the relationship between aortic and pulmonary diastolic pressures. Among the eight babies from 6 weeks to 3 years of age in whom the aorta was catheterized via the patent ductus four had a pulmonary artery mean pressure 75 per cent of the aortic or more, and four had a pulmonary artery mean pressure 50 per cent of the aortic or less. All the former had a systolic murmur alone and all the latter a continuous murmur, irrespective of their individual ages. The same relationships seem to hold true at all ages.

There is no apparent correlation between the level of pulmonary artery pressure and heart size, x-ray appearance of the pulmonary vasculature, or the electrocardiogram. Furthermore, even those who have a marked pulmonary hypertension commonly have electrocardiograms which display evidence of left rather

than right ventricular hypertrophy. The systemic blood pressure appears to be one of the most important clinical findings in this regard. Characteristic of patent ductus arteriosus, in contrast with pulmonary stenosis and interauricular septal defect for example, is a wide amplitude of the peripheral pulse pressure even in the presence of tachycardia or even congestive heart failure. The reason for this is the lowering of aortic diastolic pressure as the result of the aortic-pulmonary shunt occurring throughout both systolic and diastolic phases of the cardiac cycle. The aortic diastolic pressure seems, therefore, to be dependent upon the pulmonary diastolic pressure, sufficient elevation of which will at the same time decrease systemic pulse pressure and decrease or abolish the diastolic element of the otherwise continuous murmur.

Other auscultatory findings included accentuation or reduplication of the so-called "pulmonic" second sound at the upper left sternal border in all cases and the presence of a mid-diastolic apical rumbling murmur in three. The former cannot easily be correlated with the level of pulmonary artery pressure as commonly believed, and the latter, when present, may signify an aortic-pulmonary shunt of large magnitude,[11] although its absence certainly does not exclude such a possibility.

The next important clinical determination, of prognostic as well as diagnostic value, is that of heart size, particularly the determination of single chamber enlargement. Over-all heart size in uncomplicated patent ductus arteriosus is usually stated to be normal or only slightly to moderately enlarged, marked enlargement occurring only in cases complicated by congestive failure or subacute bacterial endarteritis or endocarditis.[13] Assuming this to be true, at least in older children, the implications are twofold: (1) that a patent ductus (in older children and adults) is not usually a serious defect and (2) that the roentgenograms may not be particularly helpful in establishing this diagnosis. Of greater importance for differential diagnosis is the determination of single chamber enlargement, for which both roentgenographic and electrocardiographic criteria should be compared.

In Fig. 1 it is evident that the cardiothoracic ratio indicated some degree of cardiac enlargement in the majority of children 1 to 3 years old who had an uncomplicated patent ductus arteriosus. Of significance is the fact that by roentgenogram, at least in the anteroposterior view, even fairly marked cardiac enlargement may not be evident during the first 6 months of life because of the normally increased measurements in this age group. It is during this period (birth to 6 months) that the electrocardiogram is of particular value, showing evidence of left ventricular hypertrophy in four of the five infants of this group. It is also noted in Fig. 1 that there is apparently no direct relation between the cardiothoracic index and the presence or absence of electrocardiographic evidence of left ventricular hypertrophy.

Although there is no roentgenographic pattern pathognomonic of patent ductus arteriosus, the following findings have been considered sufficiently typical to justify a presumptive diagnosis:[13] (1) left ventricular enlargement, (2) left auricular enlargement, (3) increased pulmonary vascularity, (4) increased amplitude of pulsations of the pulmonary artery, aorta, and left ventricle.

Left Ventricular Enlargement.—From the data in Table I the following observations may be made:

1. By x-ray criteria left ventricular enlargement was detected in fourteen out of twenty patients. Of the remaining six, three showed no ventricular enlargement, and three displayed contours suggestive of either right or combined right and left ventricular enlargement.

2. Of the fourteen patients with x-ray evidence of left ventricular hypertrophy, only eight had electrocardiograms which could be interpreted as indicative of this abnormality. Four additional ones had electrocardiograms of right bundle branch block without definite electrocardiographic evidence of left ventricular hypertrophy. The remaining two had electrocardiograms which could only be interpreted as normal.

3. Two of the three infants whose roentgenograms displayed cardiac contours suggestive of right ventricular enlargement had electrocardiograms indicating left rather than right ventricular hypertrophy, while the third had right bundle branch block.

4. The three children with normal roentgenograms also had normal electrocardiograms.

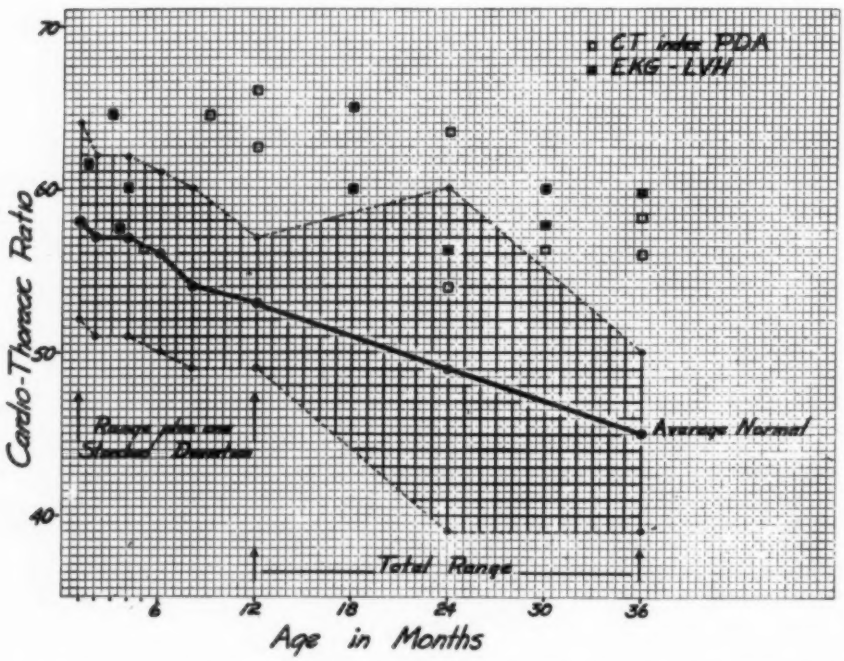

Fig. 1.—Roentgenographic and electrocardiographic findings in infants with patent ductus arteriosus. The average cardiothoracic ratio, as well as the range of normal, is indicated within the cross-hatched lines. Cardiothoracic ratio in infants with patent ductus arteriosus and electrocardiographic evidence of left ventricular hypertrophy are compared in the squared figures. It is apparent that in early infancy x-ray measurements are valueless in determining abnormal heart size. The electrocardiogram during this age period is the only means of accurately determining the presence of right or left ventricular hypertrophy. For further discussion see text.

It is important to understand the comparative value of the roentgenogram and electrocardiogram in the determination of ventricular enlargement. In the presence of normal intraventricular conduction it would appear that the roentgenogram might be the more sensitive of the two methods when the cardiothoracic ratio is less than 0.60. When the heart is enlarged to a greater degree (cardiothoracic ratio 0.60 or more), the reverse situation seems to be true, the electrocardiogram indicating left ventricular enlargement even when the x-ray contour of the heart suggests enlargement of the right rather than of the left ventricle. Although right bundle branch block theoretically should not interfere with the electrocardiographic diagnosis of left ventricular hypertrophy, it would seem from the data in Table I that this might be a possibility, and this problem will require further study. Furthermore, more accurate electrocardiographic criteria for the detection of left ventricular hypertrophy in the age group under consideration remain to be determined.

In correlation with physiological data it is noted that either x-ray or electrocardiographic evidence of left ventricular hypertrophy may occur in the presence or absence of significant pulmonary hypertension. Similarly, the presence of right bundle branch block seems to bear no direct relation to hypertension in the pulmonary circulation or right ventricle. In fact, even in the presence of pulmonary hypertension, right ventricular hypertrophy appears rarely, if ever, in an otherwise uncomplicated patent ductus arteriosus.

Left Auricular Enlargement and Increased Pulmonary Vascularity.—In this group of cases enlargement of the left auricle was only noted in those patients in whom there was fairly marked pulmonary vascular congestion. Although there are insufficient data for proof, it would appear that these findings are related to some extent at least to the degree of pulmonary hypertension. No apparent correlation could be discovered between the x-ray size of the left auricle and the duration of the P wave in the electrocardiogram. Nor was there any apparent relation between the incidence or degree of left auricular and that of left ventricular enlargement.

Amplitude of Pulsations.—Although no effort was made to evaluate this x-ray finding on a quantitative basis, it is believed that at least in this age group, it is not particularly helpful.

Certain summary facts should be emphasized with regard to the value and limitations of the roentgenogram in patent ductus arteriosus. These include the following:

1. When "characteristic," the x-ray contour of the heart and great vessels is of presumptive diagnostic value only.
2. The x-ray appearance of the heart and great vessels, especially during infancy, may either be typical of patent ductus arteriosus or may resemble that of other cardiovascular defects.
3. Conversely, the cardiovascular silhouette in other abnormalities may resemble closely that of uncomplicated patent ductus arteriosus.

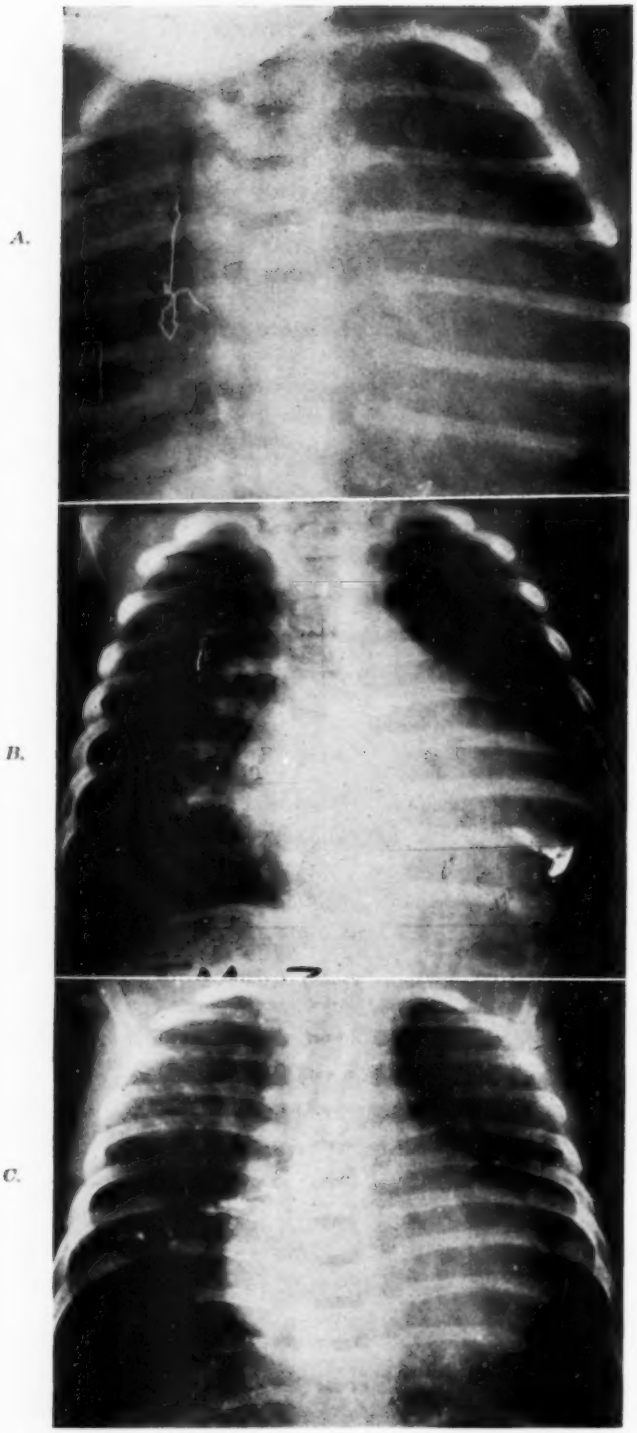

Fig. 2.—Representative roentgenograms in infants with patent ductus arteriosus. Note the wide range of individual variation in the contour of the cardiac silhouette in various infants with uncomplicated patent ductus arteriosus. Without the aid of precordial lead electrocardiograms it would be difficult, if not impossible, to state the presence or absence of right or left ventricular hypertrophy in these roentgenograms.

The roentgenograms shown may be identified as follows: *A*, Patient 1, R. L., 6 weeks; *B*, Patient 2, J. M., 3 months; *C*, Patient 3, K. Z., 3½ months; *D*, Patient 4, S. S., 4½ months; *E*, Patient 5, C. M., 9 months; *F*, Patient 6, R. R., 1 year.

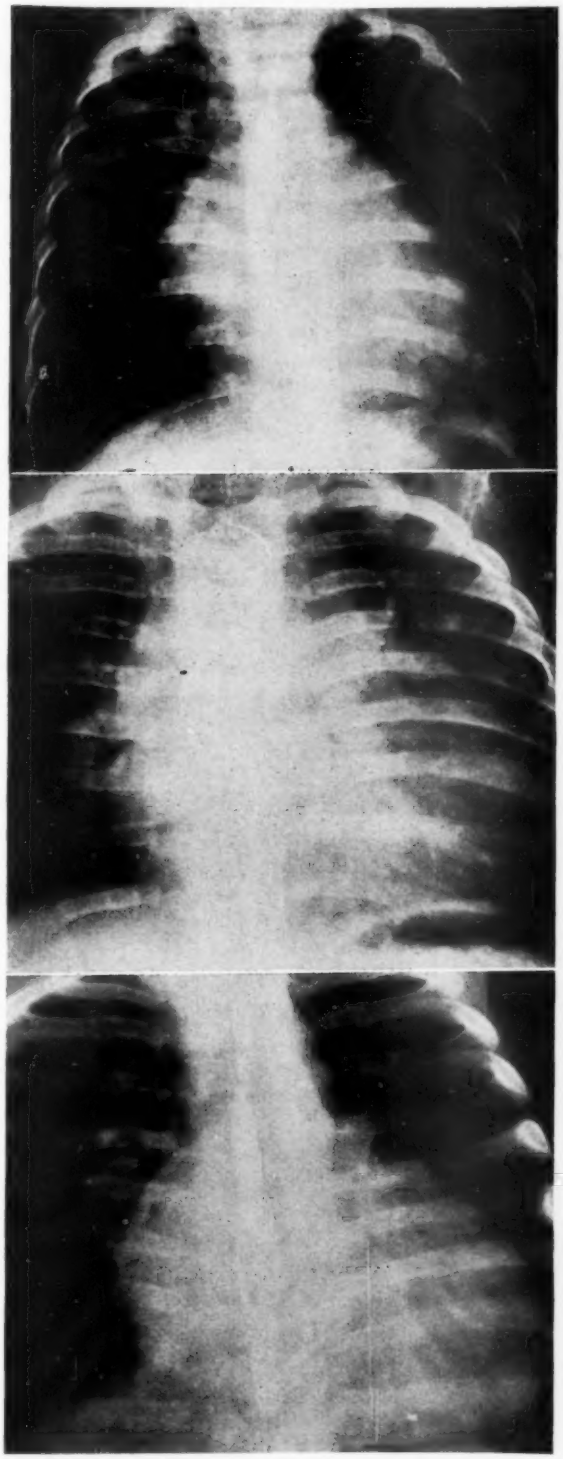

Fig. 2.—cont'd (For legend, see opposite page.)

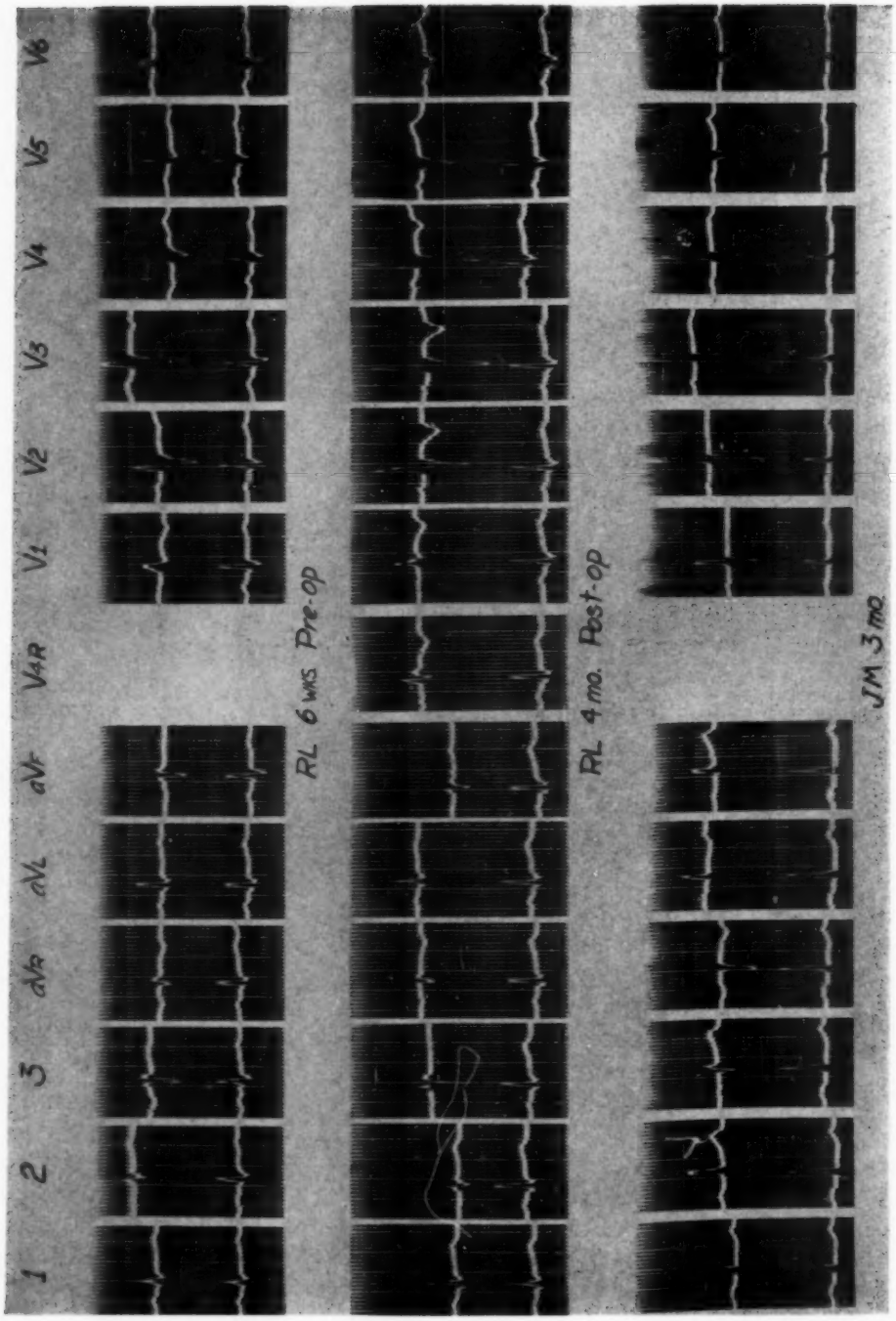

Fig. 3. A. (For legend, see opposite page.)

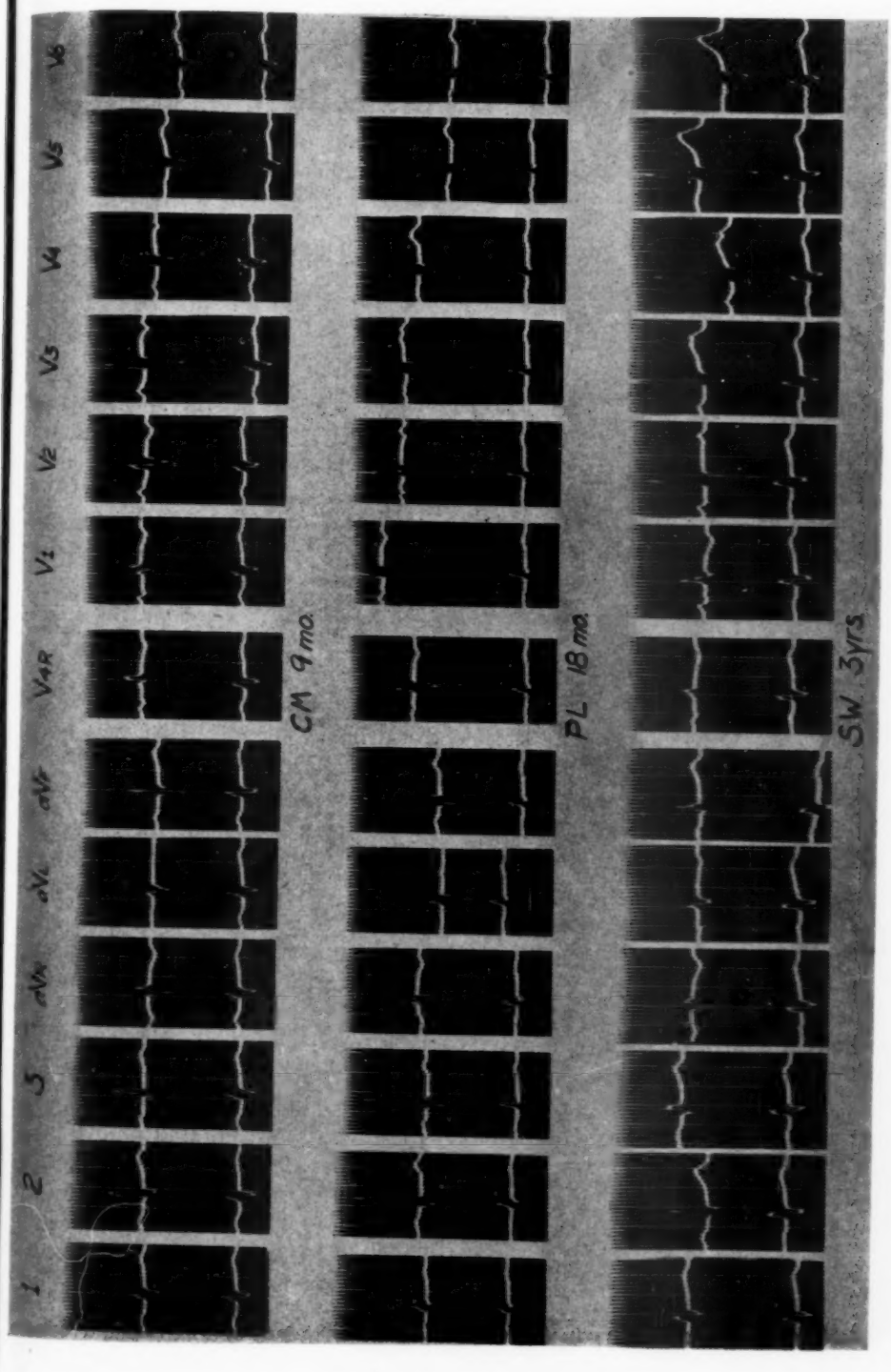

Fig. 3, *B*.

Fig. 3.—Representative electrocardiograms in infants with patent ductus arteriosus. These tracings illustrate the occurrence of two typical patterns in infants with uncomplicated patent ductus arteriosus. The first is uncomplicated left ventricular hypertrophy, the second, right bundle branch block with or without associated evidence of left ventricular enlargement. Note the discrepancy between the extremity lead findings, that is, the presence of right or left axis deviation, and the precordial lead measurements indicative of left ventricular enlargement. Right ventricular hypertrophy is notably absent except perhaps in the youngest infant (R. L., 6 weeks).

4. The determination of single chamber enlargement is most important from the diagnostic point of view; for this purpose the electrocardiogram is superior to the roentgenogram especially when over-all heart size is significantly increased.

5. The diagnosis of patent ductus arteriosus having been established, the determination of heart size (both by roentgenogram and electrocardiogram) has important prognostic and therapeutic implications.

Mention should also be made of special x-ray techniques such as angiocardiography and retrograde angiography by which the diagnosis of patent ductus arteriosus as well as other defects, such as incomplete aortic septum and coarctation of the aorta, may be made.

The chief diagnostic value of the electrocardiogram is the determination of single chamber enlargement. For this purpose criteria have been formulated for determining normal hearts[32] and right ventricular hypertrophy[34] at various ages; those for left ventricular hypertrophy are now being studied. In this group of infants with patent ductus arteriosus, in contrast to similar groups of older patients, the electrocardiograms were usually abnormal, displaying evidence of either left ventricular hypertrophy or right bundle branch block. The presence of predominant right ventricular hypertrophy is so rare as practically to exclude the possibility of an uncomplicated patent ductus arteriosus at any age and is thus of great value in differential diagnosis.

It is interesting to speculate on the frequency of left ventricular hypertrophy in the electrocardiograms of infants as compared with the much lower incidence in older children with patent ductus arteriosus. It seems possible that it might signify one of two things: (1) that the electrocardiographic diagnosis of left ventricular hypertrophy can be made more easily in infants than in older children because of factors related to the changing ratio of right to left ventricular mass with growth and development or (2) that patent ductus arteriosus is a more serious defect in early infancy and is consequently associated with a greater degree of cardiac enlargement, those surviving to later ages representing the ones with less serious defects and less cardiac enlargement.

The significance of right bundle branch block is uncertain. It is important at least to know that it can and frequently does exist in uncomplicated patent ductus arteriosus, especially in infants and young children.

Cardiac catheterization was done in ten of the twenty-two infants with patent ductus arteriosus, and in eight of these the aorta was entered via the patent ductus. If it be accepted that mean pulmonary artery pressure equals one-sixth of mean aortic pressure, then some degree of pulmonary hypertension was present in every patient with patent ductus arteriosus in whom cardiac catheterization was done. In one-half of those in whom the ductus itself was entered, the pulmonary artery pressure was 75 per cent of the aortic or higher. With regard to the occurrence of pulmonary artery hypertension in uncomplicated patent ductus arteriosus, the following correlations of importance should be noted:

1. Marked pulmonary hypertension (75 plus per cent of aortic) occurred in children without as well as in those with evidence of congestive heart

failure, thereby suggesting the possibility of two basic factors in the pathogenesis of pulmonary arteriolar hypertension: (a) primary—increased pulmonary artery resistance due to either functional vasospasm or structural changes, such as obliterative endarteritis, arteriolar medial hypertrophy, or possible atherosclerosis; and (b) secondary—left ventricular failure and elevation of pulmonary venous pressure. Pulmonary "capillary" pressures were not recorded in these patients, nor were postoperative observations recorded.

TABLE II. DIAGNOSTIC CRITERIA FOR PATENT DUCTUS ARTERIOSUS IN INFANTS

CRITERIA FOR PRESUMPTIVE DIAGNOSIS

Clinical

1. Long, harsh systolic murmur with maximum intensity at the upper left sternal border.
2. Accentuation or reduplication of the second heart sound at the upper left sternal border.
3. Continuous or systolic and diastolic murmur present or absent.
4. Wide amplitude of the peripheral pulse (palpation) even in the presence of tachycardia or congestive cardiac failure; *exception:* marked pulmonary hypertension.

Roentgenographic

1. Gross cardiac enlargement, especially with the contour of left ventricular enlargement.
2. Enlargement of the left auricle.
3. Increased pulmonary vascularity, especially in combination with left ventricular hypertrophy.
4. Increased amplitude of pulsations of the main trunk and major branches of the pulmonary arteries, aorta, and left ventricle.

Electrocardiographic

1. Greater degree of relative left ventricular enlargement than expected for age.
2. Left auricular enlargement with or without delayed auriculoventricular conduction.
3. Absence of predominant right ventricular hypertrophy, especially without associated evidence of some degree of left ventricular enlargement.
4. Possible presence of right bundle branch block, complete or incomplete, particularly in infancy.

CRITERIA FOR CONCLUSIVE DIAGNOSIS

Cardiac Catheterization

1. Direct catheterization of the patent ductus.
2. Oxygen content higher in the pulmonary artery than in the right ventricle.
3. Pulmonary artery pressure normal or more frequently increased.
4. Absence of complicating pulmonary stenosis or coarctation of the aorta.

Contrast Visualization—X-Ray

1. Retrograde aortography—simultaneous visualization of aorta and pulmonary arteries.
2. Angiocardiography—direct visualization of the ductus.

2. Marked pulmonary hypertension in this age group occurred in the absence of any accompanying electrocardiographic evidence of right ventricular hypertrophy.

3. Marked pulmonary hypertension was invariably associated with a significant reduction in aortic oxygen saturation, even in the absence of any other complicating cardiovascular defect, indicating thereby a bidirectional shunt probably occurring at different phases of the cardiac cycle.

TABLE III. DIFFERENTIAL DIAGNOSIS OF CONGENITAL CARDIOVASCULAR DEFECTS IN INFANTS

	AUSCULTATION			X-RAY AND ECG			CARDIAC CATHETERIZATION	DIAGNOSIS
	NONE	SYSTOLIC	SYSTOLIC AND DIASTOLIC OR CONTINUOUS	RVH	LVH	Rt. BBB		
Patent ductus arteriosus		+	+		+	+	Direct catheterization of ductus; increased PA oxygen content and pressure	Clinical and physiological studies
Cardiopathy of infant born to diabetic mother	+	+			+		Absence of shunt	Spontaneous reversibility
Incomplete aortic septum			+		+		Same as patent ductus	Retrograde angiography
High interventricular septal defect		+	+	+	+		Increased RV and PA oxygen content	
Coarctation of aorta		+			+	+		Clinical: blood pressure differential
Endocardial fibroelastosis	+	+			+			Pathological
Anomalies of coronary arteries	+	+			+			Pathological (electrocardiogram)
Glycogen storage disease	+	+		+	+			Pathological (metabolic)
Avitaminoses	+	+		+	+			Clinical: therapeutic reversibility

Patent ductus *plus* Tricuspid atresia			+		+		Inability to enter right ventricle	Angiocardiography
Tetralogy of Fallot			+	+			Decreased PA pressure; increased PA oxygen content; short circulation time	Physiological studies
Tetralogy plus left ventricular hypertrophy			+	+	+		Same as tetralogy	
Coarctation of aorta								
Ductus proximal			+		+		Same as ductus	Blood pressure differential
Ductus distal		+	+	+			Decreased aortic oxygen content; normal right brachial artery oxygen content	Physiological studies, angiocardiography
Pulmonary hypertension plus shunt reversal		+		+			Same as coarctation + patent ductus arteriosus distal	Physiological studies, angiocardiography
Interauricular septal defect		+	+			+	Ductus + increased RA oxygen content	Physiological studies
Interventricular septal defect		+	+		+		Ductus + increased RV oxygen content	Physiological studies
Pulmonary valvular stenosis (plus insufficiency)		+	+	+			Decreased PA pressure; absence of shunt	Physiological studies
Pulmonary endarteritis		+		+			Pulmonary hypertension; absence of shunt	Physiological studies, x-ray
Interauricular septal defect		+		+		+	Increased RA oxygen content	Physiological studies
Interventricular septal defect (mid)		+					Increased RV oxygen content	Physiological studies
Communication between aortic sinus of Valsalva and right ventricle			+	+			Increased RV oxygen content	

4. Clinical congestive heart failure in infants with a patent ductus occurred only in the presence of marked pulmonary hypertension and electrocardiographic evidence of left ventricular hypertrophy but without necessarily any significant elevation of right auricular pressure, indicating the importance of left ventricular failure and pulmonary vascular congestion.

5. The relation between pulmonary artery hypertension and the presence or absence of a continuous murmur has already been discussed under the auscultatory findings in patent ductus arteriosus.

It is important to emphasize the fact that cardiac catheterization can be done safely and easily even in small infants. This fact achieves practical significance in establishing the diagnosis of patent ductus arteriosus in infants and in detecting the presence of such complicating defects as pulmonary stenosis and coarctation of the aorta.

RESULTS OF TREATMENT

Of the twenty-two babies with uncomplicated patent ductus arteriosus there were two deaths; one (S. S., aged 4 months) died of congestive heart failure prior to any attempt to operate and one (K. K., aged 18 months) of cardiac arrest during the induction of anesthesia for attempted operation. Thus, twenty were operated on with no mortality, all recovering uneventfully after successful suture ligation of the patent ductus.* The postoperative morbidity in this age group was also low, the only complications being one case of transient left vocal cord paralysis and one case of pulmonary atelectasis which cleared slowly but completely. One child had a residual diastolic murmur after operation, as indicated in Table I. The usual period of hospital convalescence postoperatively was two weeks or less.

It is also important to note that even under full therapeutic digitalization one baby (K. Z., aged 3½ months) went into severe pulmonary edema which required almost immediate operation as a lifesaving procedure. This infant as well as the other who died preoperatively in congestive failure even though digitalized illustrates the important fact that in patent ductus arteriosus in infants, especially with marked cardiac enlargement, one is not safe in accepting even the best medical management including therapeutic digitalization as an absolute safeguard against terminal pulmonary edema. Early operation is the lifesaving procedure, not of choice, but of necessity.

It would not be fair to conclude this section without stating that in the age group under consideration three babies were explored surgically and found not to have a patent ductus arteriosus. The first, and the only one who died, had a high interventricular septal defect instead of a patent ductus and died as the result of an avoidable surgical error. The second was explored in the full knowledge that something more complicated than a patent ductus was present but in the hope that some clinical benefit could be obtained by ligation of even a small ductus. No ductus was found, but no harm was done through surgery; neither has any further diagnosis been established. The third child was one who had all

*All operations were done by Dr. Conrad R. Lam, Henry Ford Hospital.

of the classical findings, including physiological data, of a patent ductus arteriosus but on surgical exploration proved to have an incomplete aortic-pulmonary septum instead. It may be stated without qualification that such errors in diagnosis, which should occur less frequently with increasing experience, do not detract from the advisability of early surgery in infants or young children in whom the diagnosis of patent ductus arteriosus is proved or even strongly suspected and in whom there is considered to be any possible danger of terminal cardiac failure.

DISCUSSION

These observations on patent ductus arteriosus in infants provide a somewhat new perspective of the problems involved. First of all, it is apparent that an uncomplicated patent ductus arteriosus may be and frequently is a more serious defect in early infancy than in later childhood. This, of course, does not mean that all infants with a patent ductus necessarily show cardiac enlargement, congestive failure, and so forth. It seems probable that these simply represent the group which comes under medical observation because they are so obviously in need of help. There may be many others who have a systolic murmur, a normal heart size, and a normal electrocardiogram and who go undiagnosed because they do not require a complete investigation including cardiac catheterization or retrograde angiography. Some of these who are not recognized early (or are wrongly diagnosed as having septal defects) may go on to the typical clinical picture of an uncomplicated patent ductus as known in older children or the ductus may occasionally close spontaneously. Of course, after they have survived to the age of from 3 to 5 years because of the benign nature of the defect, it is obvious that the prognosis should be good excluding such unpredictable complications as subacute bacterial endarteritis. The important thing is to recognize the fact that an uncomplicated patent ductus *may* be a serious defect in infancy, that it *can* be diagnosed accurately, and that an operation *should* be done in such cases.

Granting that an accurate diagnosis can be made in infancy, and age should be no deterrent to either the necessity or the possibility of diagnosis, the next problem is when may surgical interference be considered justifiable? In order to answer this question satisfactorily, answers must first be provided for each of the following questions:

1. What is the surgical risk involved in this age group?
2. What are the medical indications for surgical interference?
3. What are the chances of a pathologically patent ductus arteriosus closing spontaneously?

As already stated, the surgical, or rather the anesthetic, mortality in this group of twenty-two patients 3 years of age or younger was less than 5 per cent, the surgical technique itself being successfully completed in every case in which it was started. The postoperative morbidity was also low and the convalescent period uniformly short. It seems fair to conclude, therefore, that the operative risk, in experienced hands at least, is not greater than in older children of the so-called "preferable" age group.

The indications for operation, as judged by the incidence and degree of cardiac enlargement and the occurrence of congestive heart failure, appear to be more urgent in early infancy than at practically any other age. In this regard it is important to remember that terminal pulmonary edema is not necessarily prevented by apparently satisfactory medical management. Closure of the ductus, either spontaneously or surgically, is the only means of removing the dangers resulting from the abnormal circulatory dynamics of this type of defect. Surgical closure is also the only means of preventing such complications as septic or aseptic thrombosis or rupture of the ductus. Subacute bacterial endarteritis, an indication for operation at any age, is apparently uncommon in infants and young children. In summary, the principal indications for operation on patent ductus arteriosus uncomplicated by any other cardiovascular defect, especially during infancy and early childhood, may be considered to include the following: (1) growth failure, otherwise unexplained; (2) cardiac enlargement, moderate or marked; (3) any evidence of cardiac failure, particularly pulmonary vascular congestion; (4) significant degree of pulmonary arterial hypertension (except when the main direction of the shunt is from pulmonary artery to aorta); (5) complicating subacute bacterial endarteritis; (6) any evidence, clinical or physiological, of a ductus shunt of large magnitude; (7) aneurysm of the ductus; (8) prophylaxis against thrombosis or rupture of the ductus.

With regard to the possibility of spontaneous closure of a pathologically patent ductus arteriosus there is little reliable information available. A number of cases have been reported in which spontaneous closure was believed to have occurred as late as 34 years of age.[6,16] Anatomical data have also been published concerning the time of closure of the ductus in infants and children without evidence of heart disease.[9] Even with these data, however, several important factors must be considered: (1) The possibility of late spontaneous closure of a pathologically patent ductus cannot be predicted on the basis of physiological closure of a "normal" ductus. (2) The number of proved cases of spontaneous closure of a pathological patent ductus are too few to anticipate such an occurrence with any degree of probability. (3) To delay operation with any anticipation of possible spontaneous closure would be the same in every respect as to delay operation for any other reason and would be attended by the same risks during the period of waiting.

The arguments which may be advanced in favor of early operation in uncomplicated patent ductus arteriosus in infants and young children include the following: (1) the ability to establish an accurate diagnosis in this age group; (2) the high mortality rate in unoperated infants with this defect, especially as compared with the low mortality rate of operation; (3) the frequency of growth impairment, cardiac enlargement and congestive heart failure, and significant pulmonary hypertension, as well as the occasional occurrence of thrombosis and rupture in this age group; (4) the low incidence of spontaneous closure of a pathologically patent ductus arteriosus; (5) the low surgical morbidity and mortality among infants and young children in experienced surgical hands.

SUMMARY

A correlative analysis of clinical and laboratory data has been made in a group of twenty-two infants from the age of 6 weeks to 3 years with uncomplicated patent ductus arteriosus.

Observations are cited which are believed to support a number of important conclusions among which are the following:

1. The diagnosis of uncomplicated patent ductus arteriosus *can* be made clinically at any age.
2. Diagnostic findings, such as the type of murmur, systemic blood pressure, and heart size, are analyzed and explained in terms of physiological data.
3. Some of the most important factors in differential diagnosis of congenital cardiovascular defects in infants are outlined.
4. Reasons are given for believing that an uncomplicated patent ductus arteriosus may be and frequently is a serious defect in infancy.
5. Surgical results in this group of infants support the belief that operation can be done safely and successfully in the age group under consideration.

ADDENDUM

Since the completion of this paper, two additional cases of uncomplicated patent ductus arteriosus in infants have been added. The first, a female infant aged 5½ months, had a continuous murmur, wide peripheral pulse pressure, marked cardiac enlargement with cardiac decompensation and retardation of normal growth, and an electrocardiogram of right bundle branch block with left ventricular hypertrophy. The second, also female, was 8 months of age and had a continuous murmur, normal heart size by roentgenogram and electrocardiogram, normal growth, and absence of any evidence of congestive heart failure. In the light of observations reported in this study neither of these two infants required cardiac catheterization, and both were operated on successfully.

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AN UNUSUAL MECHANISM OF SUDDEN DEATH IN CONGENITAL HEART DISEASE

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CHILDREN with congenital heart disease usually die of anoxemia, congestive cardiac failure, or some intercurrent illness. Among the anomalies in which anoxemia is commonly the cause of death Taussig[1] has included the tetralogy of Fallot, extreme dextroposition of the aorta, complete transposition of the great vessels, and an underdeveloped or nonfunctioning right ventricle. Among the disorders in which congestive cardiac failure is often the cause of death, Taussig[1] has mentioned the tetralogy of Fallot, complete transposition of the great vessels, an anomalous origin of the left coronary artery from the pulmonary artery, auricular septal defect, Lutembacher's syndrome, and aortic atresia. Serious intercurrent infections, subacute bacterial endocarditis, and rupture of anomalous arteries constitute the terminal illnesses in other children with congenital disturbances of the cardiovascular system. Cerebral thrombosis is a hazard to those children with anoxemia severe enough to result in polycythemia. Finally, in an appreciable number of cases, sudden death is the terminal event. This type of outcome has been observed in aortic stenosis,[1] Ebstein's disease,[2] and idiopathic cardiac hypertrophy,[3] as well as in other lesions. We have recently observed two patients with cyanotic congenital cardiac lesions in whom valvular stenosis or atresia apparently led to the formation of thrombi in isolated segments of the great arteries. These thrombi increased in size by accretion until the resulting interference with vital circulatory pathways produced sudden death.

CASE REPORTS

CASE 1.—A white female infant was born on Oct. 8, 1948, after an uncomplicated pregnancy. The birth weight was 8 pounds, 3 ounces. The delivery was normal, and there was no cyanosis at birth. Cyanosis appeared four hours after delivery and persisted thereafter; it was aggravated by crying or straining. On Oct. 12, 1948, at the age of 4 days, the infant was transferred from the maternity hospital to the Milwaukee Children's Hospital.

Physical Examination.—The patient was a comparatively large infant. The skin had a rather constant dusky hue. There was distinct cyanosis of the nail beds, lips, mucous membranes, face, ears, hands, and plantar surfaces of the feet. There were no abnormal pulsations nor distended veins in the neck. The examination of the lungs disclosed no abnormalities. There was no cardiac enlargement, precordial pulsation, nor thrill. The first and second heart sounds were particularly loud along the lower left sternal margin and were well heard at the base. There was a soft, blowing, Grade 1, systolic murmur along the left sternal margin. The cardiac rhythm was regular and 130 per minute. No clubbing of the fingers or toes was found. The remainder of the examination was negative.

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Laboratory Data.—The blood count revealed 11,200 leukocytes per cubic millimeter. The erythrocyte count was 5,050,000 per cubic millimeter. The hemoglobin was 19.0 Gm. per 100 c.c. The urine was normal. The blood Kline reaction was negative.

Radiographic and fluoroscopic examination of the thorax on Oct. 13 and Oct. 14, 1948, disclosed a heart which was slightly enlarged. Its configuration was somewhat boot shaped, the apex was elevated above the left diaphragm, the pulmonary segment was concave, and the lungs appeared abnormally clear. Re-examination of the heart on November 16 disclosed considerable enlargement of the heart, primarily of the right ventricle. The final roentgenographic examination of the thorax on Nov. 27, 1948, disclosed gross cardiac enlargement with elevation of the apex above the diaphragm and an abnormally translucent pulmonary window (Fig. 1).

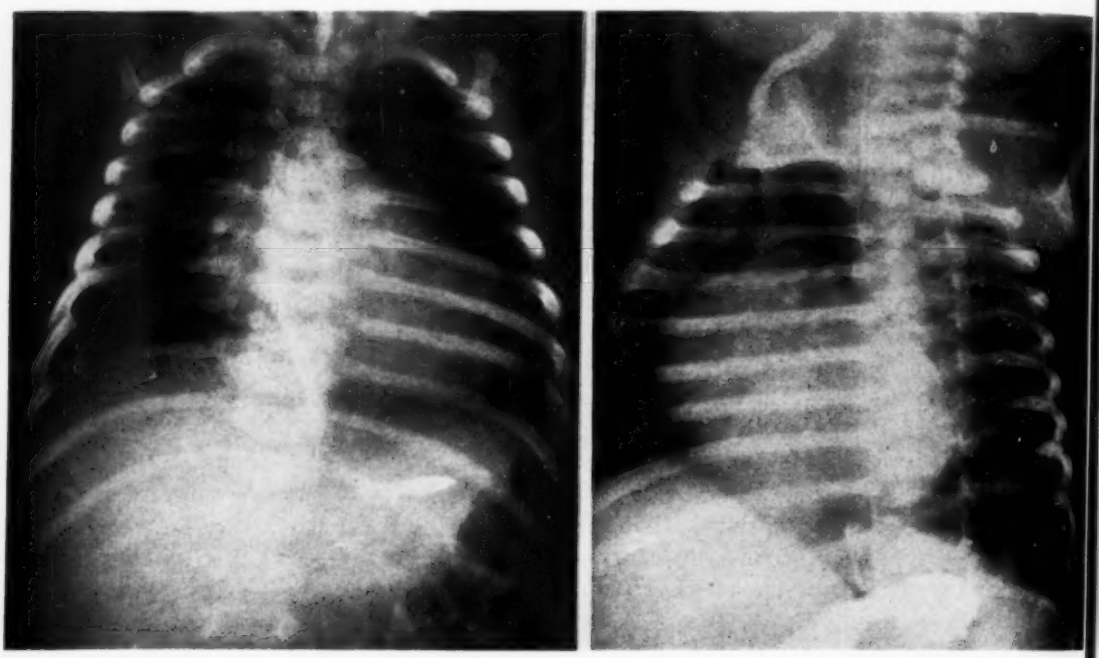

Fig. 1 (Case 1).—Roentgenograms of a female infant with pulmonary atresia, tricuspid stenosis, and a patent ductus arteriosus with a thrombus in the isolated segment of the pulmonary artery which obstructed blood flow into the pulmonary circulation. These studies made on Nov. 27, 1948, three weeks prior to sudden death, show gross cardiac enlargement, a boot-shaped silhouette, inconspicuous pulmonary vascular markings, and a translucent pulmonary window.

The electrocardiogram taken on Oct. 12, 1948, (Fig. 2) disclosed a P-R interval of 0.10 second, a QRS complex of 0.06 second, and a heart rate of 155 per minute. The mean electrical axis was approximately plus 90 degrees; the axis deviation index was minus 7. The P waves were tall and peaked in Leads II and III. The multiple precordial electrocardiograms showed changes in Leads V_1 and V_2 which were strongly suggestive of incomplete right bundle branch block and possibly right ventricular hypertrophy. The standard leads taken on Nov. 26, 1948, showed a P-R interval of 0.09 second, a QRS complex of 0.06 second, and a heart rate of 175 per minute. The right axis deviation had increased in degree. The mean electrical axis was approximately plus 120 degrees; the axis deviation index was minus 16.

The child was considered to have cyanotic congenital heart disease and it was felt that a tetralogy of Fallot was most probably the anomaly present.

Hospital Course.—The infant remained in the hospital for one month, during which time the cyanosis persisted. The child developed diarrhea and fever on one occasion which subsided in two days. At the age of 10½ weeks she died suddenly. The general condition of the patient five minutes prior to death was apparently as good as at any time during the entire hospital stay.

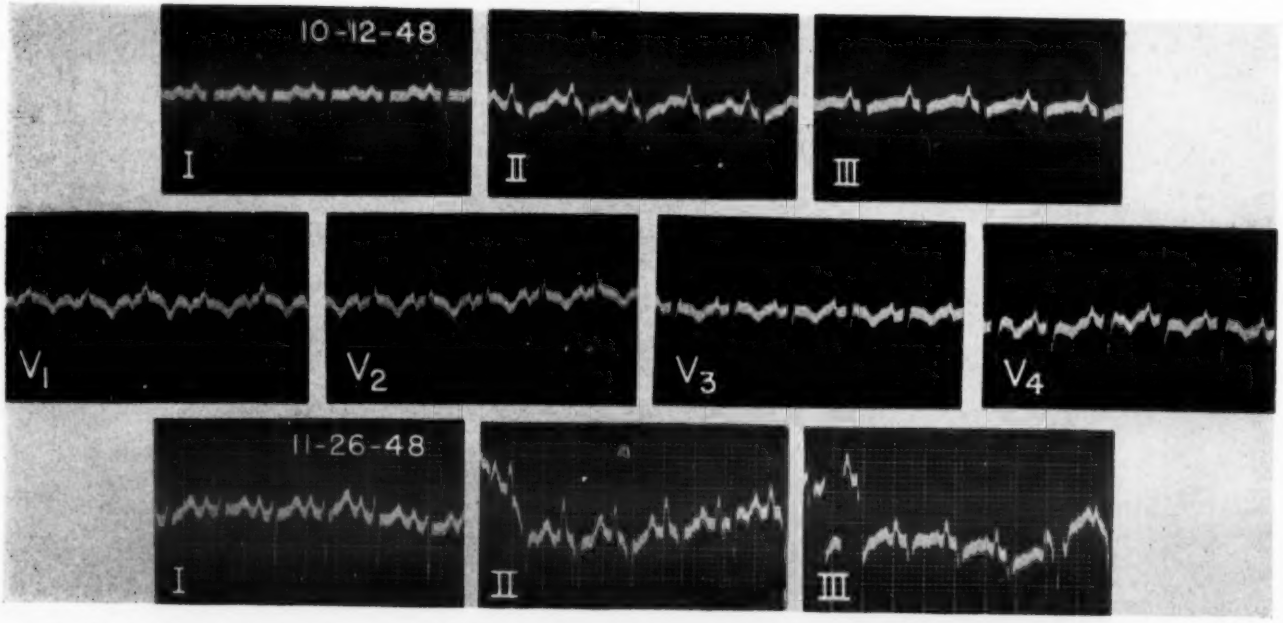

Fig. 2 (Case 1).—Oct. 12, 1948: The standard and multiple precordial electrocardiograms show evidence strongly suggestive of incomplete right bundle branch block and possible right ventricular hypertrophy. Nov. 26, 1948: The standard leads show greater right axis deviation and taller, more peaked P waves than were present in the earlier tracings.

*Post-mortem Examination.**—The significant findings were confined to the circulatory system. The heart weighed 55 grams. The mitral valve measured 4.5 cm.; the aortic valve measured 3.0 cm.; the free wall of the left ventricle measured 0.6 cm. in thickness. The right ventricular myocardium averaged 0.9 cm. in thickness; there was complete atresia of the pulmonary valve; the tricuspid valve was stenotic and had an estimated diameter of 1.0 cm. The cusps of the tricuspid valve contained hard calciferous material. The right auricular wall was thickened and averaged 0.2 cm. in thickness; the right ventricular cavity was very small, measuring approximately 1.5 cm. in diameter. The foramen ovale was patent and was 1.0 cm. in diameter. The interventricular septum was intact. The ductus arteriosus was patent and measured 0.3 cm. in diameter. At the point where the ductus arteriosus entered the pulmonary artery there was a thrombus which measured 1.0 cm. in length and 0.4 cm. in width. The thrombus was attached to the intima of the pulmonary artery at the orifice of the ductus arteriosus. The thrombus nearly filled the pulmonary artery and was situated so that it prevented blood flow from the ductus arteriosus into the pulmonary circulation. The great vessels were normal in position. When the pulmonary artery was opened from above, the fused cusps of the pulmonary valve were seen. It was not possible to pass a probe from the right ventricle into the pulmonary artery, the aorta, or the left ventricle (Fig. 3).

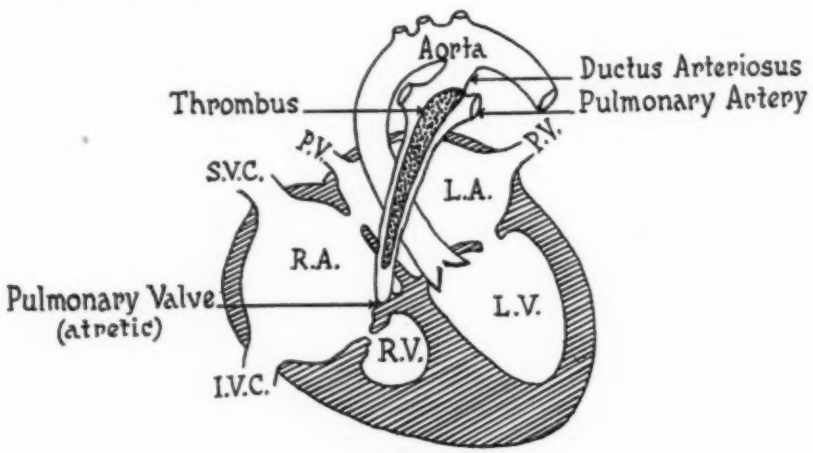

Fig. 3 (Case 1).—Diagram illustrating anomalies disclosed by post-mortem examination. Note pulmonary atresia, tricuspid stenosis, small right ventricular chamber with hypertrophy of right ventricular myocardium, and patent ductus arteriosus. The thrombus which developed in the isolated segment of the main pulmonary artery had grown large enough to obstruct the flow of blood from the ductus arteriosus into the pulmonary arterial branches.

Microscopic examination of the myocardium revealed hypertrophy and irregular fibrosis. A section taken through the base of the tricuspid valve showed calcium deposits associated with edema and increased vascularity. Examination of a section of the thrombus removed from the pulmonary artery disclosed that it was comparatively recent and laminated in character.

CASE 2.—A 3-year-old white boy was first found to have cyanosis of the nail beds and mucous membranes at the age of 17 days. On Sept. 16, 1946, at 10 months of age, the child was admitted to the Milwaukee Children's Hospital for diagnostic studies. The prenatal history was uneventful, the delivery was normal, and the birth weight was 6 pounds, 10 ounces. The family history was not contributory.

Physical Examination.—On admission the child appeared thin, undernourished, and underdeveloped. The head was large, and the superficial veins of the scalp were prominent. There was definite cyanosis in a rather patchy distribution in the midforehead and at the angles of the nose. The thorax was symmetrical, but there was distinct anterior prominence of the sternum,

*Performed by Dr. Gorton Ritchie.

particularly in its upper portions. The lungs were normal. Examination of the heart disclosed a diffuse apical impulse but no thrill. There was no cardiac enlargement. The cardiac sounds were well heard in all areas. There were no murmurs. The cardiac rate and rhythm were normal. The edge of the liver was felt 3 cm. below the right costal margin. One of the most striking findings was a distinct difference in color in the two upper extremities. There was definite cyanosis and slight clubbing of the fingers of the left hand and the toes of both feet. The right hand and arm had only a tinge of cyanosis and minimal clubbing of the fingers.

Laboratory Data.—The leukocyte count was 12,600 per cubic millimeter. There were 6,700,000 erythrocytes per cubic millimeter. The hemoglobin was 16.5 Gm. per 100 c.c. The differential blood count and sedimentation rate were normal. The blood nonprotein nitrogen was 59.7 mg. per 100 c.c. The hematocrit was 57 per cent. The urinalysis revealed 1 plus albumin but no other abnormalities.

Radiographic and fluoroscopic examination of the thorax on Sept. 18 and Sept. 19, 1946, disclosed a small heart located in the midline (Fig. 4). The transverse diameter of the heart was 6.2 cm., and the transverse diameter of the thorax was 14.0 cm. The configuration of the heart was normal. The esophagus was of normal contour when it was outlined with barium. The lungs were normal.

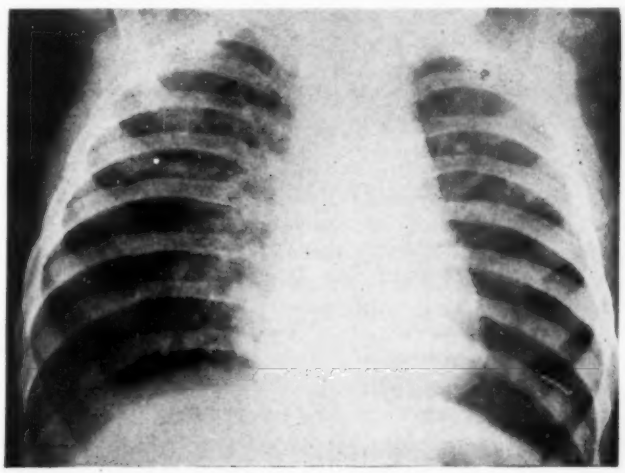

Fig. 4 (Case 2).—Roentgenogram of a male child with aortic stenosis, mitral stenosis, partial coarctation of the aorta, and a patent ductus arteriosus. A thrombus which developed in the segment of the aorta between the stenotic aortic valve and the area of coarctation was apparently responsible for sudden death twenty-six months after this film was made. This roentgenogram of the thorax made on Sept. 18, 1946, shows a heart of normal size, although its configuration at the base is unusual.

The electrocardiograms recorded on Sept. 18, 1946, disclosed a cardiac rate of 150 per minute, the P-R interval was 0.09 second, and the QRS complex was 0.06 second (Fig. 5). The standard leads showed right axis deviation. The mean electrical axis was approximately plus 120 degrees, and the axis deviation index was minus 11. The P wave in Lead II was rather tall and peaked. The precordial leads suggested right ventricular hypertrophy with reversal of the usual pattern of the precordial electrocardiogram.

Subsequent Course.—The child was discharged from the hospital with a diagnosis of congenital heart disease, type undetermined. He was considered unsuited for any operative procedure available at that time. The cyanosis and clubbing persisted but did not become worse. On Jan. 7, 1949, at the age of 3 years, the boy was brought to the Milwaukee Children's Hospital and pronounced dead on arrival. It was learned that the child had had a slight respiratory infection for one week. On the evening before admission, the boy vomited once, and that night he seemed restless. At 3 A.M. the mother noted that the child had stopped breathing.

*Post-mortem Examination.**—The body was 89 cm. in length, poorly developed and undernourished. There was cyanosis of the lips, eyelids, ears, and fingernails. Marked clubbing of the fingers and toes was present. The liver extended 10 cm. below the xiphoid process and 5.5 cm. below the costal margin in the right anterior axillary line. The thoracic and peritoneal cavities each contained a few cubic centimeters of clear amber fluid.

When the chest cavity was opened, the veins of the thorax and the right auricle were found to be markedly distended. The pericardium contained 10 c.c. of clear yellow fluid. The heart weighed 90 grams. The aortic valve was stenotic, and its orifice was only 0.2 cm. in diameter; the mitral valve orifice was abnormally small and measured 3.0 cm. in diameter; the left ventricle averaged 0.9 cm. in thickness. The tricuspid valve measured 8.0 cm. in diameter; the pulmonary valve measured 5.0 cm. in diameter; the right ventricle was 0.7 cm. in thickness. The ductus arteriosus was patent; it was in the usual position and measured 0.4 cm. in diameter and 0.5 cm. in length.

The cut surface of the entire myocardium was yellow, streaked with brownish red. The right ventricular chamber was much larger than the left. It measured 4.0 cm. in diameter, whereas the left ventricular chamber was 1.5 cm. in diameter. The atrioventricular valves were normal except for the small size of the mitral valvular orifice. The pulmonary valve was normal. The aortic valve was stenotic; only two cusps were present, and these were markedly thickened. Both of the coronary ostia were behind the aortic cusp which was adjacent to the pulmonary artery. Attached to the aortic surface of the other cusp, there was a thrombus which extended along the aorta to a point just beyond the orifice to the left subclavian artery, a distance of 4.0 cm. The thrombus was lying free in the lumen of the aorta and was attached only at the stenotic aortic valve. The great arteries came off the aorta in a normal fashion; in consequence their orifices were partially obstructed by the thrombus lying free in the aortic lumen (Fig. 6).

An atypical coarctation of the aorta was present between the origin of the left common carotid and the left subclavian arteries. Peripheral to the narrowing the aorta was slightly enlarged. Measurements of the aorta were as follows: 3.0 cm. above the aortic valve the aorta was 2.7 cm. in circumference; at the area of constriction the aorta measured 1.8 cm. in circumference; just distal to the ductus arteriosus the aorta was 4.4 cm. in circumference; the thoracic aorta was 3.2 cm. The circumference of the ductus arteriosus was 1.9 cm.

Microscopic examination of the myocardium revealed hypertrophy, edema, and slight hydropic change. There were areas of perivascular inflammatory infiltration, made up mainly of monocytes and neutrophils. In one coronary artery there was a small amount of fragmented thrombus material. This was recent since it was not attached to the vessel wall. Some subendocardial fibrosis was present. Study of a section of the thrombus found in the aorta disclosed that it was recent and laminated. The inner portion of the thrombus appeared considerably older than the outer segments.

DISCUSSION

In the first case the pulmonary atresia with persistence of a segment of the main pulmonary artery produced a cul-de-sac which opened only into the main pulmonary arterial branches and the ductus arteriosus. Because of the complete pulmonary atresia, the child was dependent for life upon the functional integrity of the ductus arteriosus. It seems probable that in the short segment of the pulmonary artery above the point of atresia there was relative stagnation of blood. This stagnation probably led to the formation of a thrombus which ultimately grew large enough to occlude the pathway from the ductus arteriosus into the pulmonary arterial branches. The obstruction to the pulmonary circulation which resulted simulated the effect of simultaneous bilateral embolism of the main pulmonary arteries, and it is consequently easy to understand why death was so sudden in this patient. The tricuspid stenosis and open foramen ovale

*Performed by Dr. Gorton Ritchie.

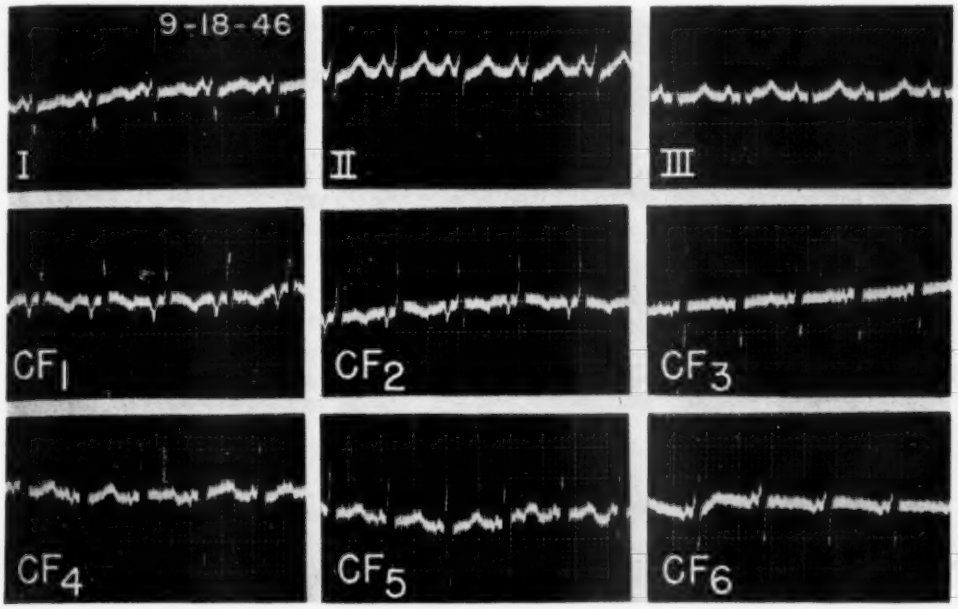

Fig. 5 (Case 2).—Sept. 18, 1946: The standard and multiple precordial electrocardiograms show changes suggesting right ventricular hypertrophy. However, when the child died suddenly twenty-six months later, the major anomalies were aortic stenosis and mitral stenosis.

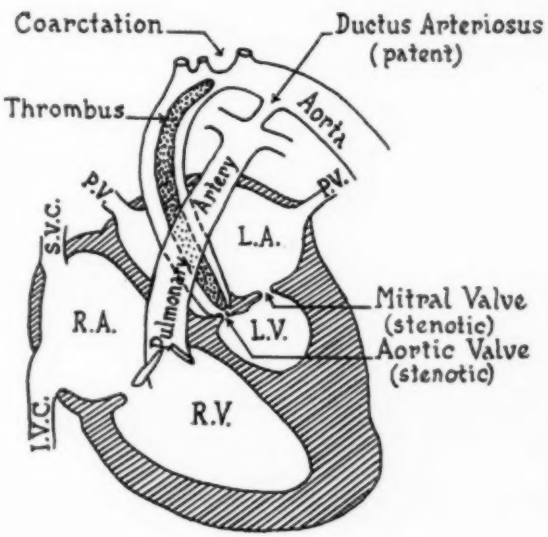

Fig. 6 (Case 2).—Diagram illustrating the anomalies disclosed by post-mortem examination. Note aortic stenosis, mitral stenosis, small left ventricular chamber, patent ductus arteriosus, and atypical coarctation of the aorta. The thrombus which had developed in the segment of the aorta just above the aortic valve had grown large enough to interfere with the flow of blood into the innominate and left common carotid arteries, apparently thereby resulting in sudden death.

combined with the pulmonary atresia produced, in effect, a nonfunctioning right ventricle. This patient represents an instance in which closure of the ductus arteriosus, either spontaneous or surgical, would have been fatal. Although we have encountered no cases exactly similar to this in terminal mechanism, Abbott mentions rupture of aneurysms of the ductus arteriosus and embolism from thrombi within them.[4]

In the second case the thrombus had developed in a zone of the aorta between a markedly stenotic aortic valve and a point of partial coarctation of the aorta. It is possible that the combination of mitral and aortic stenosis led to a lower pulse pressure than normal, thereby promoting thrombus formation. Pooling, relative stagnation, and peculiar eddies just above the anomalous aortic valve may have contributed to this development. On the other hand, one might expect forceful ejection of blood through the stenotic orifice to prevent clot formation. Although there are several possible terminal mechanisms in this case, it seems most probable that death occurred in this child when the thrombus grew sufficiently large to occlude the orifices of the major arteries, thereby reducing blood flow into the innominate and left common carotid arteries and producing fatal anoxia of the vital centers. It seems possible that the horizontal position of the child while asleep enhanced this sequence of events. It is possible, also, that the aortic stenosis alone may have produced a fatal outcome, but there was no valvular deformity of the type which would make possible a locking of the valve cusps as suggested by Van de Veer.[5] It may be that the thrombus was large enough to obstruct the output of the left ventricle sufficiently to produce death. Marvin and Sullivan[6] described a case in which sudden death apparently resulted when a narrowed aortic orifice was blocked by a thrombus attached to one margin of the valve, whereas Lutembacher[7] reported a case in which a small aortic opening was obstructed by a thrombus attached by a pedicle to the interventricular septum. Finally, it must be mentioned that coronary arterial obstruction by the small fragment of thrombus which lodged in one of the coronary arteries may have been fatal, but actually it was so small that it does not seem to have been of sufficient consequence to have killed the patient. There was no evidence of myocardial infarction, although death may have occurred too quickly for this to develop. It is postulated that the fragments in the coronary artery arose from the thrombus in the aorta and passed directly into the coronary circulation through the coronary ostia.

SUMMARY

Two cases of cyanotic congenital heart disease are reported in which an unusual mechanism seems to have operated to cause sudden death. In one patient the major lesions were pulmonary atresia and tricuspid stenosis. In the second patient the chief anomalies were aortic and mitral stenosis. In both instances thrombi developed just above the anomalous semilunar valves and ultimately grew large enough to obstruct vital circulatory pathways and produce a sudden fatal termination. As surgical procedures are developed for the alleviation of congenital anomalies, it is possible that care will have to be taken to avoid the creation of cul-de-sacs in which thrombi may form and lead to serious consequences at a later date.

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EMETINE THERAPY AND HEART DISEASE

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UNTIL recently, emetine has been the only effective drug in extraintestinal amebiasis. The introduction of chloroquine for the treatment of the hepatic phases of the disease has not entirely supplanted this time-honored drug, and it still has a place in the treatment of some phases of hepatic amebiasis and of other extraintestinal manifestations. It is useful, too, in certain other parasitoses. The continued importance of this drug has prompted the author to report his experiences with patients requiring emetine despite the presence of contraindicating heart disease.

The present data were obtained from a general study[1] of the toxic effects of emetine in 111 patients. Of these, ninety-four, or 84.7 per cent, had hepatic amebiasis; eleven, or 9.9 per cent, colonic amebiasis of a refractory type in which emetine was used in combination with other drugs; and six, or 5.4 per cent, nonamebic disease in which emetine was the drug of choice. In the entire group there were five instances of symptomatic intoxication, three of the neuromuscular variety and two of the cardiovascular type. Minor symptoms were excluded from this evaluation. In the three patients in the neuromuscular group, one had, in addition, a tachycardia, one nausea and vomiting, and the third diarrhea along with nausea and vomiting. In the cardiovascular group, one patient had tachycardia and a marked reduction in blood pressure, the other tachycardia, vertigo, and syncope. One of these showed electrocardiographic changes attributable to emetine.

All five of the patients with symptoms of emetine intoxication had normal hearts previous to and following therapy.

In the entire group of 111 patients there were eight in whom advanced heart disease was present before emetine was administered. The drug was given because it was thought that the condition requiring its use was a greater threat to life than the heart disease, and no other therapeutic agent was available. Of the eight patients, five had arteriosclerotic and one each hypertensive, congenital, and rheumatic heart disease. Of the five with arteriosclerotic heart disease, four had signs of cardiac enlargement, and the fifth, along with one of the others, had previously had congestive heart failure. Both of these were under digitalis therapy. Two of the patients were women. The ages of the arteriosclerotic group were 62, 65, 69, 69, and 72 years and the total doses of emetine administered 11, 6.9, 5, 12, and 8.8 mg. per kilogram of body weight, respectively.

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The patient with hypertensive heart disease, a 63-year-old woman, had cardiac enlargement, an abnormal electrocardiogram, and a history of previous congestive failure. The patient with congenital heart disease, a man in the twenties, had findings typical of interventricular septal defect and an electrocardiogram showing bundle branch block. The man with rheumatic heart disease, 21 years old, had findings typical of mitral stenosis, a normal mechanism, and a past history of congestive heart failure. At the time of treatment he was under digitalis therapy. In all three of these patients the total dose of emetine was 10 mg. per kilogram of body weight or less.

In seven of the eight patients with cardiac disease, electrocardiograms were taken during emetine therapy. All the tracings but one, that of the 72-year-old man with arteriosclerotic heart disease, were abnormal before emetine was started. Significant change as the result of emetine administration was recognized in one instance only. None of the eight patients developed symptoms or signs of heart failure during or after treatment, and in none of the eight were significant changes of any type noted in the cardiovascular system.

In the follow-up periods two deaths were noted, one three and one-half months and the other one year following emetine therapy. Both, we believe, were unrelated to the drug. The death at three and one-half months occurred in one of the women with arteriosclerotic heart disease. Autopsy disclosed severe coronary sclerosis with marked narrowing of the anterior descending branch. Furthermore, the interval between treatment with emetine and death, the absence of symptoms and signs during the three and one-half months, and the lack of electrocardiographic evidence of damage attributable to emetine make it difficult to consider emetine a factor in the patient's death.

DISCUSSION

Emetine has a direct effect on normal heart muscle, although these changes are not necessarily correlated with symptomatic features. When the total dose/weight ratio of emetine did not exceed 10 mg. per kilogram of body weight in the group of 111 patients from which the eight cases were derived, 26.4 per cent of the patients demonstrated electrocardiographic changes characterized by significant lowering or inversion of the T waves in one or more leads. These changes, which are indicative of the effect of the drug upon the heart, began to appear as early as the third or fourth day of treatment. The electrocardiographic findings were not accompanied by tachycardia nor by clinical evidences of myocardial insufficiency and were, therefore, not considered contraindications to further use of the drug. When the course of treatment was continued to completion under these circumstances, no ill effects were noted, indicating that such changes are not necessarily the forerunners of symptomatic cardiovascular intoxication. In the one patient who showed electrocardiographic changes who also had symptomatic cardiovascular intoxication, the drug was immediately discontinued as it was in all patients showing symptomatic intoxication.

Our experience is similar to that of others. Cottrell and Hayward,[2] in following 250 patients under treatment with emetine, found no evidences of

myocardial insufficiency. In three of Charters' patients[3] who had slight electrocardiographic abnormalities before emetine, presumably due to the severe general effects of the disease, improvement occurred after emetine. Heilig and Visveswar[4] reported similar effects.

Even when large doses of the drug are given, effects on the heart may not be evident. In one of the patients with marked neuromuscular symptoms, a tremendous amount of emetine had been given. The author saw the patient for emetine intoxication after she had received elsewhere 22 gr. of the drug in eight days. An electrocardiogram at the time was normal, as was the clinical examination of the heart. A repeat electrocardiogram two months later was unchanged.

Our experience, therefore, indicates that patients demonstrating electrocardiographic changes during therapy may usually continue their course of treatment, under careful observation, until the total course of 10 mg. per kilogram of body weight is completed. Only once in this series did a symptomatic cardiovascular picture develop when medication was continued after electrocardiographic changes had appeared. In general, no prediction could be made as to which patients would develop cardiovascular symptoms, and, when one of the several systems often involved in intoxication was affected, even to severe degree, there was no evidence of involvement in one or both of the others.

It is possible that in individuals with normal hearts emetine could affect myocardial function extensively without the appearance of tachycardia or heart failure. Histologic damage has been described as the result of emetine poisoning. It is obvious from studies on experimental animals[5] that electrocardiographic changes may be seen within one minute after intravenous emetine, an indication that a biochemical lesion may be responsible without histologic damage. How extensive such changes may be before they adversely affect myocardial function in patients whose cardiac reserve is great is debatable. However, administration of the drug to patients with definite heart disease and a known reduction in reserve to the point where failure has previously existed and is being prevented by digitalis therapy might throw some light on the problem. The present group of patients includes such examples; yet none of them developed symptoms or signs of heart failure, and only one showed the usual, but here additional, electrocardiographic changes.

CONCLUSIONS

1. The usual moderate T-wave changes which occur during emetine therapy were not, in themselves, an indication to stop treatment in the dosage schedules used in this study.

2. The definite effects of emetine upon the heart would indicate that this drug should not be used in patients with cardiac disease unless the condition for which it is being used is a greater threat to life than the heart disease, and then only when no other therapeutic agent is satisfactory.

3. When it was elected to use emetine in the presence of heart disease in this study, a total dose of no more than 10 mg. per kilogram of body weight

produced adequate clinical results and did not adversely affect the heart as far as we could determine. One patient died after three and one-half months, the death apparently being unrelated to the emetine therapy.

4. The number of patients with heart disease involved in this study is not great enough for statistical generalization.

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COMPARISON OF THE EFFECTS OF VERATRUM ALKALOIDS AND OF HEXAMETHONIUM BROMIDE UPON THE BLOOD PRESSURE IN ARTERIAL HYPERTENSION

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OUR object is to compare the effects of veratrum alkaloids and hexamethonium bromide in patients with arterial hypertension, particularly in regard to blood pressure falls, toxic effects, and suitability for continued control of blood pressure levels.

The clinical use of veratrum preceded detailed knowledge of its pharmacology. In 1835, Osgood[1] recognized veratrum as an emetic which caused the pulse to be "small, compressible and infrequent," and, in 1860, Baker[2] described the successful treatment of a case of eclampsia. Some pharmacological studies were reported by Prevost[3] in 1866, a year before the classical publication of von Bezold and Hirt[4] in which the blood pressure fall and bradycardia after veratrine were attributed to vagal reflexes arising from the heart itself. Cramer,[5] in 1915, thought the blood pressure fall was due to a reflex from the lungs with the afferent pathway in the vagus. In 1943, Amann and Schaefer[6] confirmed Von Bezold and Hirt[4] by discovering afferent fibers in the cardiac branches of the vagus which carry bursts of electrical activity in phase with the heart beat and which can be caused to discharge continuously after veratrine. Jarisch and Richter[7] (using veratrine) and Dawes[8] (using the veratrum alkaloids protoveratrine, veratridine, and cevadine) described experiments indicating that the fall of blood pressure arises mainly from a cardiac, but to a lesser extent from a pulmonary, reflex, the afferent pathways being vagal.

Although Willson and Smith[9] observed that Veratrone, a mixture of veratrum alkaloids, caused dilatation of perfused rabbit blood vessels, the evidence of Moe, Bassett, and Krayer[10] on the femoral blood flow in dogs suggests that the vasodilatation observed in the whole animal with small doses of veratrum alkaloids is brought about by reflex action. The pharmacology of veratrum, with particular reference to individual alkaloids, is admirably summarized by Krayer and Acheson.[11]

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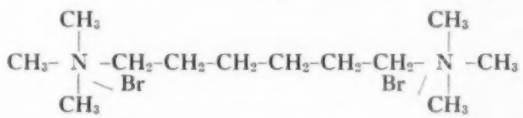
Recent publications concerning the use of veratrum alkaloids in the treatment of high blood pressure are in agreement that in some patients there are significant blood pressure falls without toxicity, and in others toxicity prevents the administration of effective hypotensive doses. Some authors[12-15] report that blood pressure falls without toxicity can be obtained in most patients, while others[16-19] find this in a minority only. An explanation of some of the discrepancies between reports on veratrum treatment may be that the classification into successes and failures depends upon the author's conception of what blood pressure falls are to be considered significant and upon the extent of fall thought to be clinically useful.

The authors cited, however, agree that there is a narrow margin between therapeutic and toxic doses, and that nausea, vomiting, and a sense of constriction in the upper thorax occur with sufficient frequency to demand most careful attention to dosage and detail of administration.

Hexamethonium bromide, similar chemically and pharmacologically to pentamethonium bromide, is a quaternary ammonium compound:



Interest in these substances began in 1868 with the work of Crum-Brown and Fraser[20] on tetraethylammonium bromide. The human and animal pharmacology of penta- and hexamethonium bromides was studied by Paton and Zaimis[21,22] and Arnold and Rosenheim.[23] The penta- and hexamethonium bromides lessen both parasympathetic and sympathetic activity, in part at least by inhibition of autonomic ganglia. The effect on sympathetic ganglia causes fall of blood pressure, "postural" hypotension, relaxation of some peripheral arterioles, and, indirectly, pulse acceleration. The effect on the parasympathetic system causes dryness of the mouth, decreased gastric juice, decreased appetite, constipation, and lessened visual accommodation.

In 1950, Restall and Smirk[24] recommended the use of the penta- and hexamethonium bromides subcutaneously in the treatment of high blood pressure. Turner[25] and Saville[26] shortly after reported blood pressure reduction following oral dosage, but were without optimism as to the practicability of the treatment. A review of further publications[27-33] indicates that in most patients subcutaneous injections give better results than oral therapy. A direct comparison of the subcutaneous and oral routes by Kilpatrick and Smirk[34] confirms this impression.

We think that hexamethonium bromide administered subcutaneously has a claim to be considered as the most widely applicable agent so far available for effective reduction of high blood pressure. A direct comparison in the same patients of hexamethonium bromide by subcutaneous injection with veratrum alkaloids by mouth seems desirable.

METHOD

Thirty-six patients received veratrum alkaloids; thirty-three of them, hexamethonium bromide (H.M.B.). Attempts at continued treatment with vera-

trum alkaloids were made in all thirty-six. Twenty-seven were treated with hexamethonium bromide for one to fifteen months, and test doses only were given to six patients. Four patients had malignant hypertension, two advanced chronic nephritis, nine pregnancy toxemia, and the remainder essential hypertension. Six patients whose blood pressures were adequately controlled on treatment with hexamethonium bromide elected to have trials with veratrum alkaloids orally; thirty untreated patients first had trials with veratrum alkaloids, and later twenty-one of them were treated with hexamethonium bromide.

The preparations of veratrum alkaloids used for oral administration were Vertavis (tablet containing 10 Craw units) and Anatensol (tablets of 0.5 mg.). The alkaloidal content of Anatensol has been published by Fried, White, and Wintersteiner.[35] Pure protoveratrine (tablets of 0.5 mg.) has also been employed. Hexamethonium bromide in 10 per cent solution was used for subcutaneous injection and as 250 mg. tablets orally.

The case numbers correspond with those employed in an earlier publication.[33]

Blood pressures were measured by the method recommended by the British and American Cardiological Societies.[36]

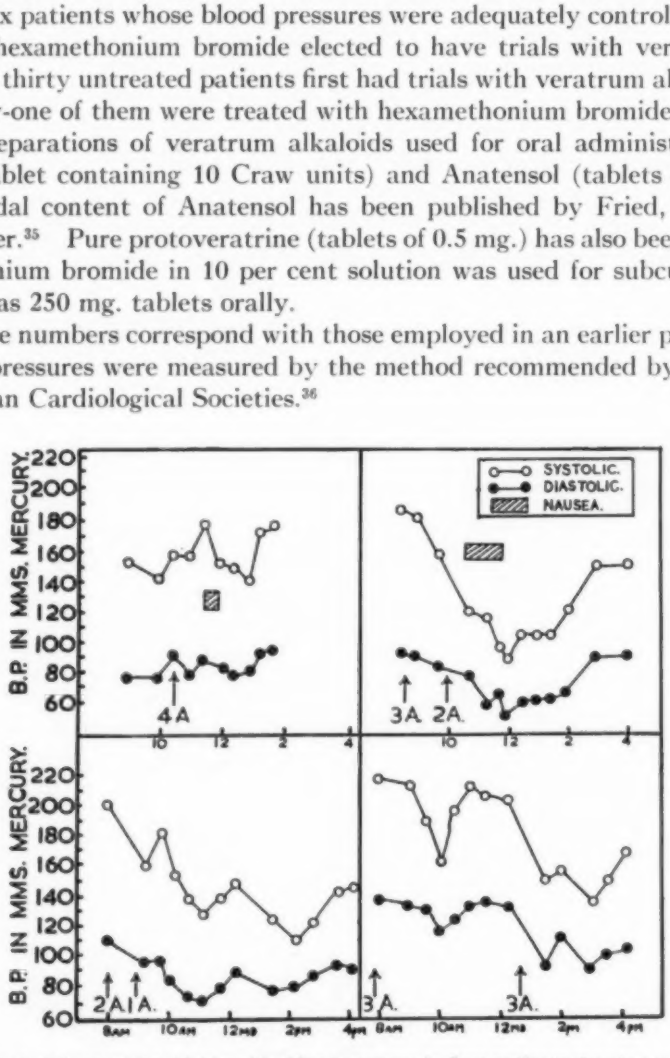


Fig. 1.—Effect of Anatensol tablets on the blood pressure in four patients showing (1) toxicity without blood pressure fall, (2) toxicity with blood pressure fall, (3) blood pressure fall without toxicity from small dose, and (4) blood pressure fall without toxicity from larger dose.

¼ *A* means four 0.5 mg. tablets of Anatensol given at the time indicated.

I. EFFECT OF VERATRUM ALKALOIDS ON THE BLOOD PRESSURE AND PULSE RATE

The hypotensive effect of veratrum alkaloids is exhibited forty-five to 150 minutes after oral administration and may last one to seven hours. Heart rates between 65 and 45 beats per minute are usual with doses which induce significant

TABLE I. MINIMAL DOSAGE OF VERATRUM ALKALOIDS PRODUCING EITHER EFFECTIVE BLOOD PRESSURE FALL OR TOXICITY

CASE NO.	MINIMAL EFFECTIVE DOSE*	RESTING BLOOD PRESSURE AND PULSE BEFORE DRUG		FALL OF BLOOD PRESSURE AND PULSE AFTER DRUG		TOXICITY WITH MINIMAL EFFECTIVE DOSE
		BLOOD PRESSURE	PULSE	BLOOD PRESSURE	PULSE	
	Patients Suitable for Prolonged Treatment					
77	3 V	180/120	78	38/22	24	NO TOXICITY
183	1½ A	198/110	74	50/24	16	
163	2: 1 A	190/110	72	64/42	30	
82	2 A	190/120	80	48/36	10	
199	2: 1½ A	190/110	68	50/20	4	
98	2: 1 V	200/120	80	80/50	8	
	2 V	168/108	80	26/16	12	
109	2 V	188/116	84	60/28	20	
103	2 V	174/102	72	38/18	12	
169	2 A	192/ 98	80	36/ 6	14	
33	2 A	210/140	80	54/30	8	
	Patients Unsuitable for Treatment					
121	3 V	222/122	72	66/14	10	Vomiting and retrosternal discomfort
63	2: 2 V	220/110	64	0/0	4	Abdominal pain and diarrhea
49	2: 1: 1 V	262/130	80	62/32	20	Lump in throat and vomiting
61	1: 1: 1 V	180/130	80	60/46	28	Lump in throat and vomiting
100	2: 1: 1 V	210/140	64	100/56	4	Choking and vomiting
28	2: 2: 2: 2 V	240/208	76	96/98	20	Faint and vomiting
113	2: 1: 1 V	290/145	64	80/37	12	Vomiting
1X	2: 1 A	200/130	84	30/18	10	Dizzy
110	2: 2 A	216/126	74	36/18	4	Retching, vomiting, and hiccups
156	2: 2 A	200/108	78	44/13	14	Vomiting and choking
55	2: 1: 2 A	260/170	92	0/10	+8	Choking
154	2: 1½ A	226/124	106	44/10	26	Nausea
105	3: 3 A	220/130	70	36/10	2	Vomiting
3X	2: 2: 1 A	172/99	60	42/15	0	Epigastric discomfort
116	2: 1 V	260/126	68	20/15	17	Nausea, vomiting, and retrosternal pain
16	2: 2: 2 A	236/138	78	40/20	6	Nausea and vomiting
167	5½ A	172/104	80	42/26	12	Strong nausea and malaise
162	3 A	192/96	64	24/0	4	No symptoms
159	6½ A	230/136	70	14/–8	0	No definite symptoms
164	5 A	194/130	80	28/14	4	No symptoms
193	2½: 1 A	224/124	72	86/34	12	Vomiting and chest constriction
2X	2: 2 V	220/124	84	20/14	12	Nausea
50	2: 2 V	264/138	84	42/25	6	Vomiting
	Patients of Doubtful Classification					
95	2: 1 A	174/108	60	40/18	10	NO TOXICITY
97	2: 2: 1 V	170/110	58	40/25	8	
72	2: 2: 1 A	180/108	84	44/20	12	

*The letter "A" refers to Anatensol tablets (0.5 mg.). The letter "V" refers to Vertavis tablets (10 Craw units).

The figures refer to the number of tablets given; where two or more figures are given, the tablets have been given at hourly intervals in the number indicated by the figures.

falls in blood pressure, and bradycardia may be apparent in some patients, indicating that the dose taken will reduce the blood pressure. Minimum pulse rate and minimum blood pressure may coincide, but often bradycardia is earlier. The relation of blood pressure fall to toxicity is mentioned later. The effects of oral Anatensol vary from patient to patient. Examples are seen in Fig. 1.

The results in Table I show that the minimum effective dose (meaning the minimum dose which produces *either* significant blood pressure lowering *or* toxicity) usually lies between 1 and 3 mg. of Anatensol and between 20 and 50 Craw units of Vertavis. Ordinarily, patients responding to small doses are more likely to have a fall of blood pressure without toxicity as an early manifestation of pharmacological activity. In patients responding only to large doses, toxicity often accompanies blood pressure reduction, subtoxic doses being ineffective in regard to the blood pressure. When the same dose is repeated in the same patient, the degree of blood pressure fall may vary (Table II), owing possibly to differences in the absorption rates brought about by meals of differing composition. For effective therapy a study of individual response is imperative.

TABLE II. VARIATIONS IN THE MAGNITUDE OF THE BLOOD PRESSURE FALL AFTER VERATRUM ALKALOIDS

CASE NO.	DATE	DOSE*	RESTING BLOOD PRESSURE BEFORE DRUG	MINIMUM BLOOD PRESSURE AFTER DRUG	MAXIMUM FALL
163	Dec. 2, 1950	2½: 1¼ V	206/118	150/80	56/28
	Dec. 9, 1950	2½: 1¼ V	180/110	110/60	70/56
82	Dec. 23, 1950	2: 1 V	190/120	140/106	50/14
	Jan. 20, 1951	2: 1 V	180/120	90/50	90/70
20	Dec. 2, 1950	2: 2: 1 A	220/125	150/85	70/40
	Dec. 9, 1950	2: 2: 1 A	230/130	220/120	10/10
77	Dec. 17, 1950	3½: 1½ A	170/110	160/110	10/0
	Mar. 15, 1951	3: 1 A	175/112	114/60	61/52
154	Jan. 19, 1951	2: 2 A	252/132	172/108	80/24
	Jan. 27, 1951	2: 2 A	254/132	136/94	118/38

*The letter "A" refers to Anatensol tablets (0.5 mg.). The letter "V" refers to Vertavis tablets (10 Craw units).

The figures refer to the number of tablets given; where two or more figures are given, the tablets have been given at hourly intervals in the number indicated by the figures.

When one of the pure alkaloids, protoveratrine, is given intravenously (Fig. 2), the blood pressure fall and bradycardia are prompt and of short duration, but do not otherwise differ from the effects of oral dosage with mixed alkaloid preparations. Delayed action after oral dosage depends on absorption. Reference to toxic effects is made in Section III.

TABLE III. CONTRAST BETWEEN VERATRUM ALKALOIDS AND HEXAMETHONIUM BROMIDE IN REGARD TO THE DEVELOPMENT OF DRUG TOLERATION FOLLOWING REPEATED ADMINISTRATION*

CASE NO.	VERATRUM ALKALOIDS						HEXAMETHONIUM BROMIDE					
	INITIAL DOSE† (TABLETS)	BLOOD PRESSURE REDUCTION		FINAL DOSE (TABLETS)	BLOOD PRESSURE REDUCTION		INITIAL DOSE (MG.)	BLOOD PRESSURE REDUCTION		FINAL DOSE (MG.)	BLOOD PRESSURE REDUCTION	
		FROM	AMOUNT		FROM	AMOUNT		FROM	AMOUNT		FROM	AMOUNT
77	2: 1 V	180/90	30/0	3 V	180/120	40/20	25	200/132	90/62	75	202/140	66/46
183	3½ A	210/130	70/30	2 A	186/108	70/30	15	220/130	56/20	50	214/130	60/18
163	3 A	200/110	78/34	2: 1 A	200/110	74/42	15	240/110	65/10	45	230/142	70/22
82	2 A	200/120	64/22	2 A	204/118	62/34	15	174/110	24/0	75	194/134	42/16
199	3 A	180/112	30/14	3½ A	190/110	50/20	30	195/120	85/30	45	195/130	70/40
109	1: 1 A	212/132	92/50	1: 1 A	232/146	70/32	10	216/130	66/18	35	196/130	94/44
103	2: 1: 1 V	190/130	56/40	2: 1½: ¾ V	190/108	70/24	20	232/132	50/22	95	204/140	40/20
121	2: 2 A	206/122	82/32	2: 2 A	206/126	84/44	15	208/138	38/8	100	198/128	40/18

*These figures should not be used to compare the extent of the blood pressure falls obtainable by the two drugs; this is done in Table VI.

†The letter "A" refers to Anatensol tablets (0.5 mg.). The letter "V" refers to Vertavis tablets (10 Craw units).

The figures refer to the number of tablets given; where two or more figures are given, the tablets have been given at hourly intervals in the number indicated by the figures.

TABLE IV. CONTRAST BETWEEN VERATRUM ALKALOIDS AND HEXAMETHONIUM BROMIDE IN REGARD TO THE EFFECTS OF CHANGE IN POSTURE UPON THE BLOOD PRESSURE

CASE NO.		VERATRUM ALKALOIDS						HEXAMETHONIUM BROMIDE					
		STANDING		SITTING		LYING		STANDING		SITTING		LYING	
		BLOOD PRESSURE	PULSE	BLOOD PRESSURE	PULSE	BLOOD PRESSURE	PULSE	BLOOD PRESSURE	PULSE	BLOOD PRESSURE	PULSE	BLOOD PRESSURE	PULSE
77	Before	186/120	84			180/120	78	220/130	68	220/130	68	230/140	64
	After	140/102	62			142/98	54	142/100	80	158/110	80	172/114	68
183	Before	216/140	98			210/130	92	200/130	72	220/132	68	214/130	68
	After	124/88	76			140/98	64	150/112	88	172/124	88	180/130	84
163	Before	200/110	71			180/110	57	220/130	72	220/122	72	210/120	64
	After	110/74	52			130/86	45	142/98	84	170/110	80	174/100	68
82	Before	200/120	84			210/140	84	188/132	84	182/124	80	200/134	80
	After	110/70	60			120/90	48	142/110	88	150/112	84	154/110	84
199	Before	218/136	78			212/132	72	210/142	60	210/140	60	220/144	60
	After	130/88	80			134/88	60	120/90	80	132/90	80	140/98	64
98	Before	184/108	92	182/100	88			224/144	72	254/160	80	210/134	68
	After	146/88	92	148/82	68			126/96	116	138/108	104	170/114	76
109	Before	186/118	88	198/118	88			190/130		196/130			
	After	128/92	80	122/90	72			104/90		114/88			
103	Before	160/110	88	180/110	88			200/140		204/140			
	After	140/92	72	136/90	60			140/110		154/118			
33	Before	220/150	92	224/150	88			222/160	96	210/140	96		
	After	100/78	64	106/84	64			110/64	112	116/78	104		

121	Before	208/132	76	212/136	68	202/130	58	220/130	92	250/140	88		
	After	118/76	72	116/76	52	124/78	50	84/58	92	100/60	88		
63	Before	252/118	74	260/120	72			180/80	88	170/78	80	160/80	80
	After	220/120	68	240/100	68			120/80	80	130/80	80	160/90	88
49	Before	260/120	80	264/130	80			232/150	80	250/154	80		
	After	204/116	72	210/120	64			142/104	112	160/108	104		
61	Before	220/130	60	210/140	60			230/140	80	230/140	80	220/160	80
	After	132/92	44	130/94	48			106/80	120	158/120	100	200/140	88
100	Before	260/160		240/160				248/155	80	230/150	80		
	After	200/130		190/134				190/150	100	220/150	80		
28	Before	210/170	80			240/208	76	180/130	74	180/130	84	210/152	82
	After	110/90	88			170/115	52	100/70	128	146/110	114	168/124	86
1X	Before	174/120	96			226/132	84	184/130	96	192/130	88		
	After	134/82	90			130/80	80	134/100	88	150/106	76		
105	Before	220/130	80	210/138	72			250/164	88	242/160	88		
	After	130/94	76	118/76	60			132/94	104	154/116	96		
162	Before	182/90	64	192/96	64			190/100	60	188/102	60		
	After	172/92	64	168/88	64			118/78	68	142/80	64		
164	Before	180/130	80	194/132	80			182/110	100	182/110	98		
	After	144/106	76	150/110	76			156/108	84	162/112	85		
193	Before	210/120	72	224/124	72			200/110		236/120			
	After	142/90	60	138/90	60			142/106		160/110			
95	Before	162/108	78	166/100	60			164/120	72	176/130	74		
	After	100/74	60	114/68	48			120/110	72	138/106	72		

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In contrast with hexamethonium bromide, it is difficult to be sure that repeated administration of veratrum alkaloids leads to drug toleration. Although an occasional patient experiences mild toleration, the dose of veratrum producing a given fall of blood pressure is seldom doubled after months of continued treatment; whereas, after continued hexamethonium bromide treatment, three to ten or more times the original dose may be needed to produce an equivalent effect (Table III).

A comparison of blood pressure levels in the lying, sitting, and standing postures is seen in Table IV, where the effects of posture on the blood pressures and pulse rates after veratrum alkaloids and after hexamethonium bromide are compared. "Postural hypotension" in patients under the influence of Anatensol or Vertavis is unimportant except when there has been excessive blood pressure lowering; then the patient may become faint on standing, and the blood pressure may fall lower.

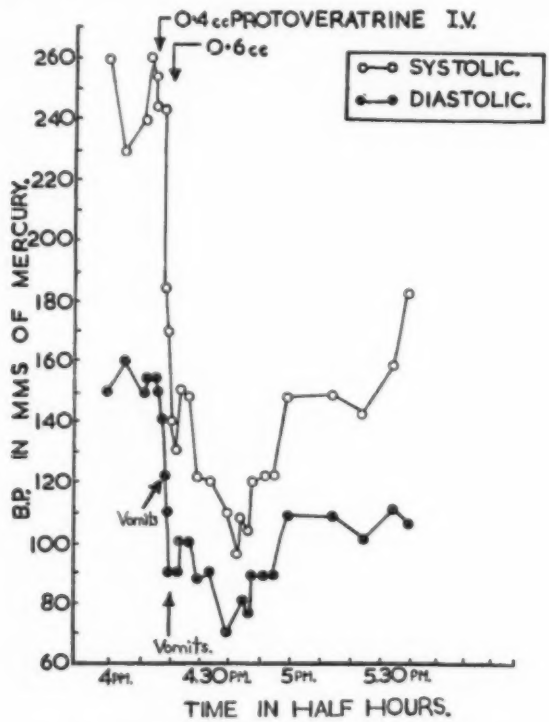

Fig. 2.—Effect of intravenous protoveratrine (1 c.c. = 0.2 mg.).

II. EFFECT OF HEXAMETHONIUM BROMIDE ON THE BLOOD PRESSURE AND PULSE RATE

Hexamethonium bromide may be administered intravenously, intramuscularly, subcutaneously, or orally. Initial oral doses of hexamethonium bromide cause falls of blood pressure, but drug toleration develops, and in most patients oral dosage after a time becomes ineffective; hence, in most patients maintenance

of effective blood pressure reduction demands a regime of subcutaneous injections as with insulin in diabetes. Some patients, however, who are very sensitive to the drug by subcutaneous injection may be well controlled by oral doses. This applies particularly to patients who have undergone sympathectomy. For oral administration a suitable initial dose is 125 mg., best given with 100 ml. of water on an empty stomach, thrice daily at about six-hour intervals. The dose is raised daily until the amount given is sufficient to induce a fall of blood pressure. Doses greater than 1 Gm. thrice daily are usually not well tolerated. Fig. 3 indicates a typical result. With oral dosage the onset of the blood pressure fall is slower than with subcutaneous injection, and the effect is usually more prolonged. Pulse acceleration may not be pronounced or may be absent.

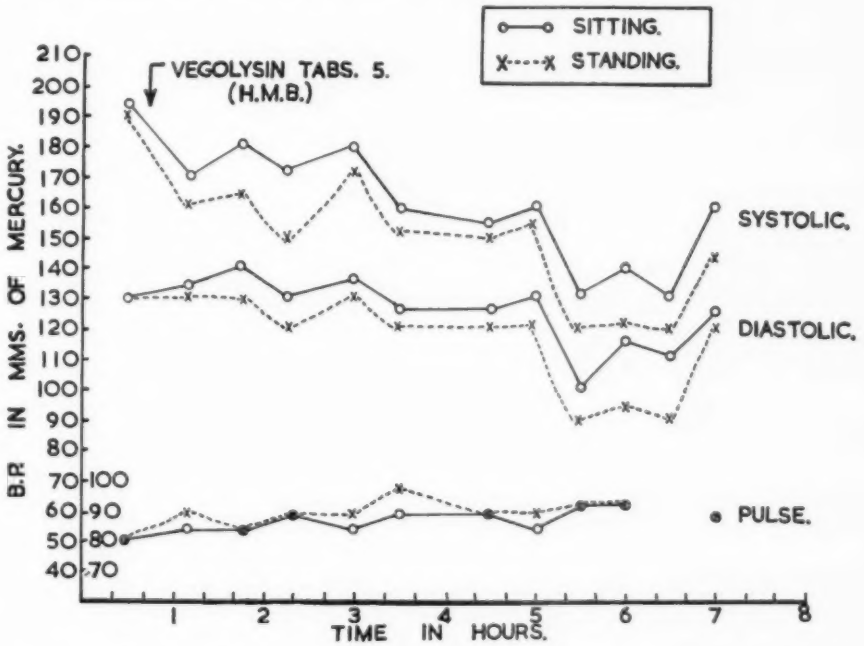

Fig. 3.—Effect of Vegolysin (hexamethonium bromide, H.M.B) 250 mg. tablets on blood pressure and pulse rate.

Drug toleration follows repeated subcutaneous injections, and the effective individual dose may rise from 15 to 200 or more milligrams as full toleration develops (Table III). The degree of toleration acquired to hexamethonium bromide is usually greater than that shown in Table III, mainly because in this new series of patients the full toleration has not developed in all patients. A more representative series in this respect, but without comparison with veratrum alkaloids, has been published elsewhere.[33]

The initial subcutaneous dose should be 15 mg. thrice daily at five-hour intervals as larger doses may be attended by hypotensive collapse before toleration develops. Subsequent dosage depends on the response to 15 mg., of which Fig. 4 is typical. The pressure fall after a single subcutaneous dose starts in a few minutes, often reaches a maximum within one-half hour, and lasts two to four

hours. The maximum fall after the larger doses given when toleration has developed is exhibited thirty to 120 minutes after the injection and often lasts longer. In the sitting posture the systolic fall after an initial subcutaneous injection of 15 mg. may range from 15 to 150 mm. Hg. Diastolic pressures commonly fall about one-third of the extent of the systolic. An overaverage response to 15 mg. (Fig. 5) is illustrative of the danger of starting with larger doses.

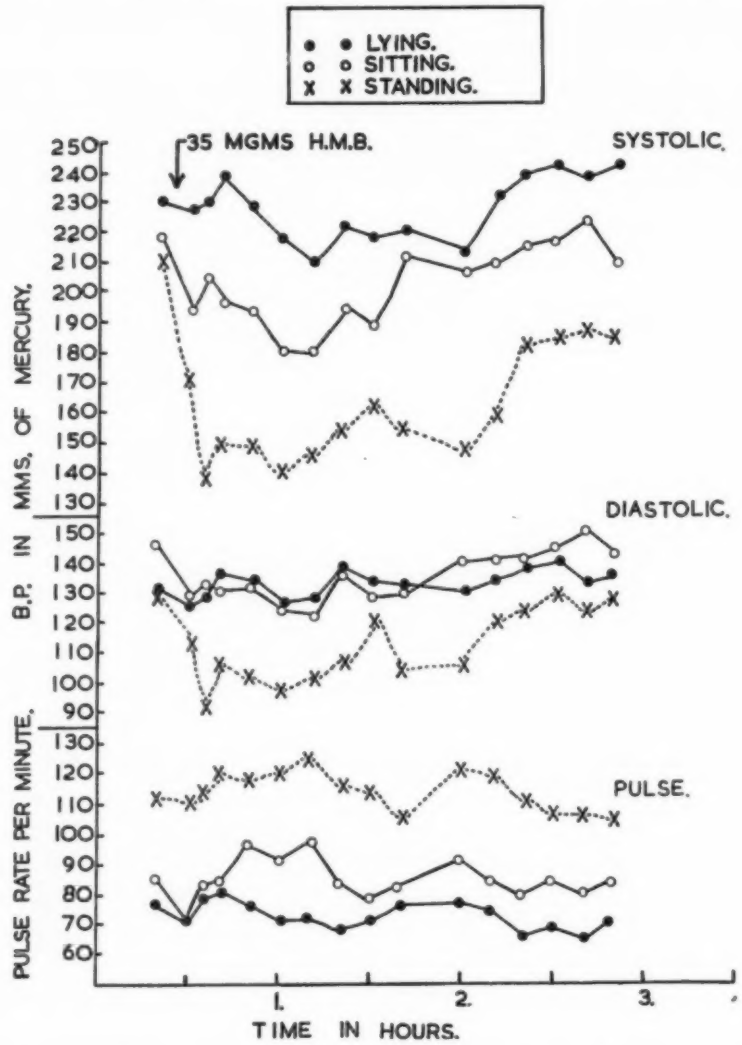

Fig. 4.—Effect of hexamethonium bromide (H.M.B.) subcutaneously on the blood pressure and pulse rate in the lying, sitting, and standing postures.

The blood pressure fall is influenced by posture (Table IV), being greatest standing, of intermediate magnitude sitting, and least lying. It is of practical importance to utilize the effect of posture to augment blood pressure falls when treating patients with hexamethonium bromide.[29] This minimizes side effects

as greater falls are obtained with less drug. With acute falls of pressure there is usually a heart rate increase which is greatest in the standing, intermediate in the sitting, and least in the lying posture, but any tendency to syncope may slow the pulse again. It has been shown elsewhere[33] that with continued treatment there is less pulse acceleration with blood pressure reduction.

With a few exceptions, our object in treatment has been to reduce the blood pressure to as near normal as is practicable. Therefore, in the course of a few weeks, the dose of hexamethonium bromide has been raised by 5 or 10 mg. every few days or as often as necessary to bring the trough of the blood pressure fall down to about 120 systolic in the standing posture. This might correspond to about 140 or 150 systolic in the sitting posture and 170 or 190 systolic in the lying position. The blood pressure level is not held at such satisfactory figures, but the average blood pressure over the day is much reduced, provided the patient spends most of the time in the sitting or standing posture or, if he is not ambulant, in a cardiac bed. The practical details of the treatment are given elsewhere.[29]

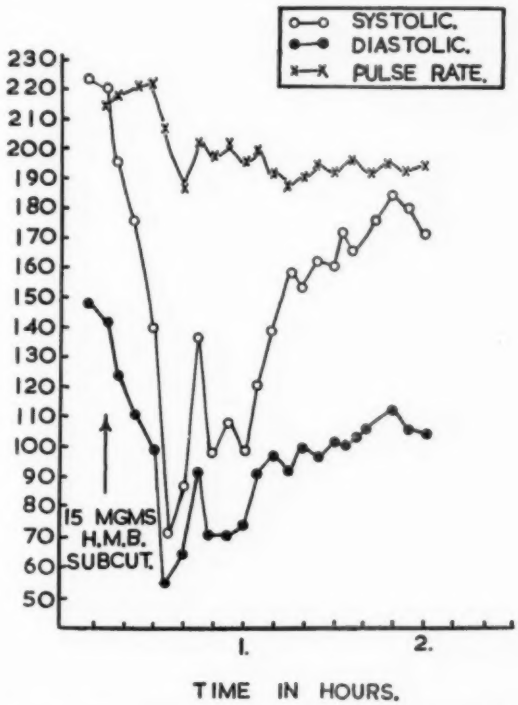

Fig. 5.—Effect of 15 mg. of hexamethonium bromide (H.M.B.) subcutaneously on the blood pressure in a patient with overaverage sensitivity to the drug.

III. TOXIC OR SIDE EFFECTS OF VERATRUM ALKALOIDS

The usual symptoms of toxicity after oral doses of Vertavis or Anatensol are nausea, pallor, and general misery, often followed by vomiting, sometimes violent and repeated. Some patients vomited without having much malaise; others were ill and unable to stand, though they recovered usually within an hour.

Diarrhea has occurred. Tingling about the fingers, lips, tongue, and feet were common but not disturbing. A frightening sensation of constriction in the throat and upper chest was common and sometimes associated with inability to swallow. Those who had this symptom often would not persist with the drug. In some instances a milder sensation, a retrosternal lump, was experienced. Retrosternal and epigastric burning sensations were sometimes mentioned. These symptoms were encountered in almost all patients during the preliminary trials with various doses, but were not present to an important degree on the treatment regime finally adopted in the patients accepted for continued therapy.

The suggestion has been made that the toxicity of veratrum alkaloids may be due to unfavorable alkaloids in the preparation used. Although there seemed to be a better separation between toxic and therapeutic effects of the pure alkaloid protoveratrine, these were still close enough to give difficulty in most patients. The toxic effects of protoveratrine injected intravenously were substantially the same as those exhibited by Vertavis and Anatensol administered by mouth. An example of the action of intravenous protoveratrine is set out in Fig. 2. Protoveratrine given orally to the point of toxicity in six patients also led to symptoms corresponding with those from the mixed alkaloid preparations, and the

TABLE V. TIME RELATIONSHIP BETWEEN OCCURRENCE OF TOXICITY AND BLOOD PRESSURE FALL

CASE NO.	DOSE*	TOXICITY	BLOOD PRESSURE AT TIME OF TOXICITY		MINIMUM BLOOD PRESSURE DURING PHASE OF TOXICITY	MINIMUM BLOOD PRESSURE DURING TEST
			FALLING	RISING		
183	3½ A	Nausea and vomiting	+		160/118	140/98
163	2½: 1 V	Constriction in throat	+		160/94	146/88
82	2: 1 V	Nausea	+		110/72	92/50
98	1: 1: ½: ½ V	Nausea	+		150/90	142/98
109	2: 1: 1 V	Nausea and vomiting	+		140/100	130/96
103	2: 1: ½: ½ V	Lump in throat	+		130/88	120/70
121	2½: 1½ A	Choking and nausea	Symptoms with maximum fall			130/96
63	2: 2 V	Abdominal discomfort	+		220/110	180/90
49	2: 1: 1 V	Retching and lump in throat	Symptoms with maximum fall		200/98	200/98
61	1: 1: 1: 1 A	Constriction of throat and vomiting	+		140/94	118/80
100	2: 1: 1 V	Choking and vomiting	Symptoms before and after maximum fall			110/80
28	2: 2: 2: 2 V	Nausea and vomiting	Symptoms with maximum fall			144/110
113	3: 2 V	Nausea and vomiting	+		180/98	160/96
110	2: 2 A	Nausea and vomiting	+		190/110	188/102
156	2: 2 A	Vomiting and choking	+		176/100	156/95
154	2: 2 A	Nausea	+		180/110	136/94
167	5½ A	Nausea and faintness	+		148/80	120/78
193	2½: 1 A	Vomiting and choking	+		182/104	138/90
95	3 V	Nausea and vomiting	+		120/80	70/48

*The letter "A" refers to Anatensol tablets (0.5 mg.). The letter "V" refers to Vertavis tablets (10 Craw units).

The figures refer to the number of tablets given; where two or more figures are given, the tablets have been given at hourly intervals in the number indicated by the figures.

description already given is equally applicable to the toxic effects of protoveratrine. In almost all instances after Anatensol, Vertavis, and protoveratrine toxic symptoms such as vomiting and chest constriction occurred while the blood pressure was falling, and ordinarily the patient was symptomless before the hypotension was most pronounced or, if not by then, before the blood pressure had risen much of the way toward the starting level (Figs. 1 and 2). Some particulars of the time relationship between toxic effects and blood pressure fall are set out in Table V.

The narrow gap between effective blood pressure reduction and toxic manifestations is an important practical difficulty. Often a significant pressure fall only occurs with or after toxicity, and, when the dose is sufficiently reduced to avoid toxicity, there is no material blood pressure fall. In more fortunate patients adjustment of the dose, with subdivided administration, makes significant blood pressure lowering practicable without important side effects.

Table VI sets out the relationship between blood pressure lowering and toxic effects after administration of oral Anatensol or Vertavis compared with the like data after hexamethonium bromide injections. Even in the patients most suitable for treatment with mixed veratrum alkaloids, the blood pressure lowering

TABLE VI. COMPARISON OF THE HYPOTENSIVE ACTION OF MIXED VERATRUM ALKALOIDS AND HEXAMETHONIUM BROMIDE

CASE NO.	MAXIMUM BLOOD PRESSURE LOWERING WITHOUT TOXIC EFFECTS		MAXIMUM BLOOD PRESSURE LOWERING WITH TOXIC EFFECTS	
	VERATRUM ALKALOIDS	HEXAMETHONIUM BROMIDE	VERATRUM ALKALOIDS	HEXAMETHONIUM BROMIDE
77	74/48 to 106/72	86/30 to 134/98	No toxic effects during trials*	No toxic effects during trials*
183	76/28 to 110/78	72/32 to 140/108	100/42 to 106/70	No toxic effects during trials
163	94/36 to 106/68	125/50 to 120/70	124/90 to 78/54	No toxic effects during trials
82	90/50 to 120/90	44/32 to 144/100	90/70 to 92/50	No toxic effects during trials
199	74/44 to 134/88	95/45 to 110/85	No toxic effects during trials	No toxic effects during trials
98	90/50 to 102/70	116/52 to 138/108	No toxic effects during trials	No toxic effects during trials
109	92/52 to 120/70	86/48 to 124/102	No toxic effects during trials	No toxic effects during trials
103	84/48 to 130/80	60/30 to 140/110	112/70 to 88/50	110/70 to 100/70
169	58/10 to 134/88	54/8 to 122/98	No toxic effects during trials	No toxic effects during trials
121	42/18 to 154/102	80/44 to 130/90	96/46 to 116/76	150/50 to 100/90
63	40/20 to 200/100	80/32 to 140/78	40/20 to 180/90	138/50 to 74/58
49	24/0 to 230/110	70/52 to 140/70	62/32 to 200/98	106/46 to 138/92
61	42/20 to 178/106	80/90 to 140/90	112/64 to 118/80	102/60 to 98/73
100	10/0 to 210/150	90/46 to 134/96	100/64 to 110/88	112/70 to 122/90
28	18/13 to 172/132	45/32 to 115/88	96/98 to 144/110	64/46 to 96/74
110	15/14 to 185/100	62/38 to 170/96	36/18 to 180/108	128/68 to 116/72
55	30/10 to 210/130	73/20 to 110/84	30/30 to 230/140	95/70 to 95/50
154	93/32 to 142/90	104/40 to 132/98	118/38 to 136/94	126/70 to 110/78
105	50/35 to 160/100	134/74 to 100/76	102/54 to 118/76	No toxic effects during trials
116	80/31 to 184/93	100/30 to 142/100	Toxic effects; blood pressure readings lost	118/42 to 146/98
16	20/8 to 164/126	142/100 to 78/60	No toxic effects during trials	No toxic effects during trials
198	58/26 to 170/110	58/10 to 142/100	86/34 to 138/90	No toxic effects during trials
71	56/10 to 164/110	42/28 to 132/98	No toxic effects during trials	84/54 to 126/86
134	52/34 to 128/96	50/50 to 122/80	54/34 to 112/80	No toxic effects during trials

*As seen in Table V, all patients had toxic symptoms at some stage, but these were not recorded during the representative trial doses on which these figures are based.

without toxicity is less than that with hexamethonium bromide. In patients unsuitable for treatment with mixed veratrum alkaloids, the magnitude of blood pressure fall without toxicity is much less.

Figures concerning maximum blood pressure falls recorded in the presence of toxicity (Table VI) are artificial, as greater falls can be induced by larger and more toxic doses of either drug. The data, however, show the pressure falls encountered in dosage trials when we overshot our aim of maximal pressure reduction without toxicity.

IV. TOXIC OR SIDE EFFECTS OF HEXAMETHONIUM BROMIDE

The toxic effects of hexamethonium bromide are qualitatively similar for subcutaneous and oral administration, but more prominent with the oral, especially those involving the alimentary tract. Constipation is more frequent with subcutaneous administration and attacks of diarrhea with oral doses. Most of the side effects to be described were encountered while attempting to regulate doses in the early stages of treatment and were absent or trivial in patients on a stable regime. It has been noted on many occasions that as doses are increased to offset the development of drug toleration, the parasympathetic effects of the hexamethonium bromide become less conspicuous than the sympathetic effects. As a consequence when, after a few months, the effective dose of hexamethonium bromide has become stable, parasympathetic side effects are usually distinctly less evident than they were at the beginning of treatment.

The effect of hexamethonium bromide subcutaneously differs from that of the mixed veratrum alkaloids in that toxic effects seldom precede an appreciable blood pressure reduction. At first with hexamethonium bromide large pressure falls in previously untreated hypertensive patients may cause faintness and pallor even if the systolic blood pressure is not fully reduced to normal. These symptoms are usually relieved promptly if the patient lies flat, for then the blood pressure rises (Table IV). When, with treatment, the patient becomes accustomed to lower blood pressures, no faintness results ordinarily, even with the pressure at normal levels or 90 systolic.

Among ninety-eight patients treated for periods of one to twenty-three months,[24,29,33] including the present series, no instance of permanent ill effect has been encountered. The side effects of subcutaneous doses, though not infrequent, seldom induce a patient with severe hypertension to end the treatment. Side effects seem to arise directly out of the known pharmacology of the substance. Excessive inhibition of sympathetic ganglia leads to excessive fall of blood pressure, with faintness, unsteadiness, and pallor, which can be regulated by altering the dose or by temporarily placing the patient in a horizontal position. Some lassitude is common during the period of maximum blood pressure fall. Sympathetic inhibition may be associated with impotence in older men and lessened sexual activity in younger men, but there is a return of sexual activity when the drug is omitted for several days. Excessive inhibition of the parasympathetic ganglia is seldom of serious moment, though achlorhydria[37] may be responsible for loss of weight and appetite and in part for the tendency to diarrhea

for several days. Certainly, during epidemics of diarrhea among the other ward patients or nursing staff, there has been an overaverage incidence of it among patients treated with hexamethonium bromide. A dry mouth occurs in most patients, and flatulent abdominal distention, sometimes with colicky pain, is not unusual in the early stages of treatment. Some blurring of the vision is usual, mainly from loss of accommodation, and dilatation of the pupils may be noted and accompanied by increased sensitivity to bright light. The blurring of the vision can often be corrected by 1, 2, or 3 diopter positive eyeglasses.

Of the thirty-six patients who attempted treatment with veratrum alkaloids, twenty-seven were given a period of treatment with hexamethonium bromide for one to fifteen months. Effective blood pressure reduction was present in all instances. Three of the twenty-seven patients on hexamethonium bromide treatment wished to discontinue for reasons set out in Sections V and VI.

V. EXPERIENCE WITH PATIENTS AMENABLE TO TREATMENT WITH MIXED VERATRUM ALKALOIDS, INCLUDING STUDIES OF THEIR RESPONSE TO HEXAMETHONIUM BROMIDE

Patients responding to trial doses of Anatensol or Vertavis by blood pressure falls without important toxic manifestations were given a period of trial treatment. Of thirty-six patients it was found possible to maintain ten on treatment for periods of three months or more. One of these patients, who had chronic nephritis, was satisfactorily controlled without rise in the total nonprotein nitrogen but developed an acute infection and died in uremia.

Experience with these ten cases indicates that continued therapy is feasible with the drug in some cases (Table I); tolerance does not develop to an important degree (Table III); toxic symptoms do not usually become more frequent as therapy continues; and most patients who have responded well for one month are able to continue on veratrum alkaloids apparently indefinitely.

Of the ten patients amenable to treatment with veratrum alkaloids, eight were given a trial period of treatment with three subcutaneous injections of hexamethonium bromide daily. This treatment was acceptable to all eight, and no important toxic manifestations were encountered. In fact, in patients responding well to veratrum alkaloids, it seemed easier to obtain symptomless control over blood pressure levels with hexamethonium bromide (Table VI).

VI. EXPERIENCE WITH PATIENTS NOT AMENABLE TO VERATRUM TREATMENT, INCLUDING STUDIES OF THEIR RESPONSE TO HEXAMETHONIUM BROMIDE

Twenty-three of the thirty-six patients could not be controlled satisfactorily by veratrum alkaloids. Usually this became apparent with test doses, but unsuitability was not decided on a single trial as the margin between therapeutic and toxic doses is narrow, so that even in the most suitable patients the magnitude of, and the time interval between, doses must be carefully controlled. In twenty of the twenty-three untreated patients it had seemed impossible on several trials to find a system of dosage producing appreciable blood pressure falls (Table I) without the toxic manifestations referred to in Section III.

In some instances the fall of blood pressure which accompanied toxicity was considerable. In four of the twenty patients a preliminary regime led to fall of blood pressure without much toxicity, but at a later stage toxicity increased, and it became impracticable to continue with further treatment. In the remaining three of the twenty-three patients, single doses of 3.2 mg. of Anatensol were without effect on the blood pressure, though no important toxic symptoms ensued. The decision not to try larger doses was therefore arbitrary.

Of the twenty-three patients definitely rejected for veratrum treatment, eighteen were treated with hexamethonium bromide for periods of one to fifteen months. Control over the blood pressure level was practicable in all. In three additional patients test doses of hexamethonium bromide were given, and the falls of blood pressure without important toxicity suggested, on the basis of previous trials,[24,33] that continued treatment with hexamethonium bromide would have been practicable if attempted. In the remaining three patients the response to hexamethonium bromide was not investigated.

Three patients remain for consideration whose suitability for continued veratrum treatment remained doubtful. One of these with renal insufficiency was unresponsive to small test doses of hexamethonium bromide, one was treated successfully, and one was not investigated.

Not all of these patients whose blood pressure levels could be controlled by hexamethonium bromide remained on treatment. One female patient, aged 44, discontinued treatment at her own request; the blood pressure rose again, and she developed a cerebral hemorrhage two weeks after treatment stopped. Death occurred from congestive heart failure three months later. This patient had experienced a sense of abdominal distention and some constipation. She was in the care of a psychiatrist for psychoneurosis, and the tolerance of side effects and of the injection regime was probably less than average. Before stopping treatment, she had had hexamethonium bromide injections for four months in the hospital, and papilledema and congestive heart failure disappeared. A second patient whose treatment was interrupted by a colonic resection for bowel carcinoma experienced frequent diarrhea and abdominal pain after hexamethonium bromide, and treatment was terminated. A third patient who had made good subjective improvement wished to avoid injections and decided to transfer to some form of oral therapy.

In the remaining patients no imporatant difficulty has arisen, though adjustment of dosage and minor alterations of the regime have been necessary in order to maintain a lower blood pressure level without important discomfort.

DISCUSSION

Only one-third to one-quarter of thirty-six patients, when given extensive trials with mixed veratrum alkaloids (Vertavis and Anatensol), had blood pressure reductions of 40 to 80 mm. Hg regularly without severe toxic effects, and, further, there seemed no way of predicting without individual trials which patient would be responsive. If, however, the patient was responsive, the blood pressure level throughout the day could usually be well controlled by spacing the doses, though mild toxic symptoms were likely to occur periodically. Moreover, veratrum

alkaloids seem to be safe in the proper doses, and no undue concern was experienced from their hypotensive action on the patients treated. Administration is easy, and, if toleration to the drug does occur, it is very slight.

Mixed veratrum alkaloids seem unsuitable for the treatment of acute cardiac complications of hypertension and encephalopathic attacks, if compared with hexamethonium bromide, for the following reasons:

1. There is only a 1 in 3.6 likelihood of the drug being effective.
2. Vomiting, retching, choking sensations, and retrosternal discomfort of the severity of anginal attacks are frequent and, when present, would prejudice the recovery of an acutely ill patient.
3. In favorable cases several days are usually required to determine the effective maintenance dose.

The main advantage of hexamethonium bromide is its reliability of action, in that treatment can be initiated with the knowledge that in patients with severe hypertension blood pressure reduction of 40 to 100 mm. Hg can be obtained safely in a few hours if urgently required. By an electrically operated syringe emptying device,[38] used in urgent cases, the blood pressure may be regulated to the desired level for as long as injection is maintained. Side effects occur, but the acute and important ones are due to the fall of the blood pressure to levels to which the patient is unaccustomed and are readily corrected. The postural swing of blood pressure (Table IV) is a safeguard, since patients are either ambulant or are treated in an upright sitting posture in bed or on a chair, and lying the patient flat will lead to an increase of blood pressure. In nearly 100 patients who have had treatment with this drug (mainly as outpatients injecting themselves) no deaths have occurred due to the drug action.

Hexamethonium bromide has disadvantages. In most patients, for reliability of action, it must be given by subcutaneous injection. If given orally, only about the same proportion of hypertensive patients can be effectively controlled as were controlled with the veratrum drugs.[34] Thus, the patient, like the diabetic on insulin, has to become accustomed to injections, usually thrice daily.

Further, the main hypotensive response from a single injection lasts two to four hours, and, as more than three injections daily are impracticable, the pressure has risen again before each injection. Methods of overcoming these rises by the use of substances to retard the drug's absorption from the tissues are to be published by one of us (F. H. S.). The fact that marked drug toleration develops in the early stages of therapy makes control more difficult, but after the first few months the dose becomes stable.

SUMMARY

1. In thirty-six patients with arterial hypertension attempts were made to reduce the blood pressure by oral administration of mixed veratrum alkaloids (Anatensol, Vertavis), and in twenty-seven of these continued treatment with hexamethonium bromide was also attempted.

2. Substantial blood pressure reduction without important toxic symptoms was possible in ten of thirty-six patients with mixed veratrum alkaloids and in all of twenty-seven patients with hexamethonium bromide injected subcutaneously. Treatment with the latter was maintained for periods of one to fifteen months.

3. Veratrum alkaloids and hexamethonium bromide resemble each other in that the therapeutic range of dosage is narrow. Graded responses can be obtained with less difficulty using hexamethonium bromide.

4. Continued administration leads to drug toleration with hexamethonium bromide, but little or no toleration develops with mixed veratrum alkaloids. The effective dose of hexamethonium bromide becomes stable after some months, and toleration does not interfere with continued treatment.

5. After hexamethonium bromide blood pressure falls are greatest in the standing, intermediate in the sitting, and least in the lying posture. After veratrum alkaloids postural hypotension is inconspicuous.

6. After hexamethonium bromide the pulse is ordinarily accelerated, but following continued treatment it may be unchanged. After veratrum alkaloids there is bradycardia.

7. The main toxic manifestation of hexamethonium bromide is faintness and lassitude associated with excessive fall of blood pressure; the symptoms are maximal when the blood pressure is at its lowest level. After veratrum alkaloids toxic effects occur while the blood pressure is still falling and may have disappeared before the blood pressure reaches its lowest level.

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PULMONARY HEART DISEASE DUE TO BILHARZIA: THE BILHARZIAL COR PULMONALE

A Clinical Study of Twenty Cases

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BILHARZIAL pulmonary heart disease is a condition that is not uncommonly seen in hospital practice in Egypt. Subjects are usually adolescent or adult male land laborers who have been suffering for many years from urinary or intestinal bilharziasis or both and who always have somatic bilharziasis. The cardiac state develops as a sequence of pulmonary embolism with ova of the Schistosoma parasites that produce pulmonary arteriolitis. The healing process which follows the pulmonary arteriolar injury results in an obliterative pulmonary arteriolitis that ultimately leads to a rise of pulmonary pressure.

The present group of twenty cases was met with in the course of a study made by Girgis and Baragan[1] on a series of 1,000 cardiac patients, of whom 500 were admitted to Fouad the 1st University Hospital and the other 500 were seen in private practice. This makes a 4 per cent incidence of bilharzial cor pulmonale among cardiac patients seen in hospital practice. No cases, however, were seen among the 500 cardiac patients seen in private practice where somatic bilharziasis is rarely met with.

PATHOLOGY

According to the work of Sorour[2] and of Shaw and Ghareeb,[3] the underlying cause of bilharzial cor pulmonale is a process of repeated embolism of the pulmonary arterioles with Bilharzia ova that are carried by means of the systemic venous blood to the right side of the heart and thence deposited in the lungs.

Embolic ova reach the systemic veins from the vesical, ureteric, prostatic, and uterine venous plexuses where they are laid by *haematobium* worms and from the portal venous system where they are laid by *mansoni* worms. The latter reach the systemic veins via anastomotic channels that develop as a sequence of hepatic cirrhosis.

The nature of the pulmonary lesion developing depends on the number of ova reaching the lungs, and it is only massive and repeated embolism of the pulmonary vessels that eventually leads to a degree of pulmonary endarteritis sufficient to raise the pulmonary blood pressure and produce a dilatation of the trunk and main branches of the pulmonary artery as well as a hypertrophy of the right ventricle.

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The ova carried to the lungs are impacted in those pulmonary vessels that are too small to allow their passage; this occurs in the arterioles accompanying the respiratory bronchioles. An impacted ovum soon escapes through the vessel wall into the lung parenchyma; it is helped in this process by the thinness of that wall and the necrotizing action of the ovum itself. When it has attained a perivascular position, a bilharizial tubercle is formed. Only rarely an ovum remains embedded in the vessel wall.

As a result of the escape of the ova through the vessel wall, an acute necrotizing arteriolitis with destruction of the media results. The injured part of the vessel wall is soon covered by endothelium, while the subendothelial tissue and media are converted into a swollen hyaline mass of necrotic debris where the ovum lies for some time before it finally escapes into the lung parenchyma. The adventitia also becomes infiltrated with mononuclear cells, and hemorrhage sometimes occurs into the necrotic vessel wall, although the endothelium seems to be intact. In spite of the destruction of the arteriolar wall, thrombosis of these vessels never occurs, and aneurysms do not develop.

The vascular lesions heal by means of a fibrocellular thickening of the intima which narrows the lumen and fills up the gap where the media has been destroyed, producing an obliterative arteriolitis. This is often followed by canalization of the occluding tissue by newly formed capillaries that sometimes dilate to produce an angiomatoid structure. This angiomatoid formation was regarded by Shaw and Ghareeb as characteristic of pulmonary bilharziasis and an adaptation to overcome the obstruction to the pulmonary circulation.

The ultimate result of this healing process is an obstruction to the pulmonary blood flow and the production of pulmonary hypertension when the lesion is widespread. Consequent to the rise of pulmonary blood pressure, the large branches of the pulmonary artery develop a condition of myohypertrophy, and still larger branches and the main trunk become the seat of atheromatous changes and dilatation that often reaches aneurysmal dimensions.

The right ventricle hypertrophies, and its walls may be as thick as 1 cm. or more, depending upon the degree of pulmonary hypertension present.

In Egypt an infection with either the *haematobium* or the *mansoni* worms can produce bilharzial cor pulmonale. The majority of cases, however, come from the region of the Nile Delta where land laborers commonly harbor not only one, but often both, parasites at the same time and where heavy parasitic infection and somatic bilharziasis are of common occurrence.

PRESENT STUDY

The age incidence in this series varied between 12 and 40 years with the average at 25 years, and the incidence in the two sexes was four males to every one female. Sixteen were land workers, and all twenty patients had spent most of their lives working on the land.

On admission to the hospital twelve were still suffering from bilharziasis, and two of these had a double infection (urinary and intestinal). The rest of the patients were free of the disease, but all gave a history of having suffered a parasitic infection.

The presenting symptoms in order of frequency were (1) dyspnea on effort, (2) palpitations, (3) a sense of dull ache in the precordial region, (4) pain in the epigastrium, and (5) cough and hemoptysis.

Clinical examination showed visible pulsations in the second, third, and fourth left intercostal spaces with a slight or a moderate degree of cardiac enlargement in twelve cases, no cardiac enlargement in six cases, and marked enlargement in two cases. In every case the heart was more enlarged as seen by roentgenogram than it was by clinical assessment because of emphysema, which is always present. A diastolic shock was felt in the pulmonary area in eleven cases; a systolic thrill was present in the same area in two cases and a diastolic thrill in one case. A harsh systolic murmur was heard in the pulmonary area in nine cases, and in six more cases both systolic and diastolic murmurs were heard in the same intercostal space. Thus, the diastolic murmur of functional pulmonary regurgitation (Graham Steell murmur) was heard in six cases. A triple rhythm was heard at and inside the apex in four cases, and the second sound in the pulmonary area was markedly accentuated in all cases. Cardiac rhythm was regular in all patients with the exception of one who had auricular fibrillation. The systemic blood pressure was invariably within normal limits. The liver was moderately enlarged and firm in fourteen cases and shrunken and firm in the six remaining cases, and the spleen was large and firm in all cases.

The blood picture showed a moderate degree of anemia with a slight eosinophilia in the majority of cases.

Only one patient had a positive Wassermann reaction.

Cyanosis was not a feature in these cases and was present only in three patients who had cardiac failure.

The x-ray appearance offered the most confirmatory evidence to diagnosis. In the anteroposterior view, the heart usually presented the picture of right ventricular enlargement in which the lower part of the left border was steeper in appearance due to the enlargement of the right ventricle and particularly of its conus portion and its participation in the formation of this border.

The pulmonary trunk was dilated and showed a marked degree of prominence and density below the aortic knob, and its right and left branches also became the seat of enormous dilatation. This was shown by the good visibility of these vessels, while their peripheral branches were especially apparent in active cases.

The right branch was usually more massive and showed as a commalike opacity descending from the hilum of the right lung, while the left branch was usually hidden by the pulmonary trunk and the conus portion of the right ventricle and could only be seen if the x-ray picture was taken with the patient's left shoulder slightly forward. Disklike opacities were often seen near the hilum on either side and were due to dilated vessels, as seen in cross section. In the active cases the vessels at the base of the lungs often showed the tortuous, beaded appearance (rosary arteries) described by Erfan and associates.[4] In these cases perivascular mottlings of the lung fields could also be seen.

The aorta was usually normal in size, but occasionally showed a slight degree of hypoplasia.

In the right oblique view the prominent shadow of the pulmonary artery encroached upon the retrosternal space anteriorly, while its right main branch, by displacing the left bronchus posteriorly, produced a marked impression on the barium-filled esophagus below the aortic indentation. The left auricle was invariably of normal size and caused no appreciable displacement of the esophagus.

In the left oblique view the aortic window was usually seen filled with the shadow of the left pulmonary branch, while the right ventricle showed a marked degree of enlargement.

Calcification of the pulmonary artery or its main branches was not seen in any of these cases.

Fluoroscopy revealed a slight to moderate degree of expansile pulsations of the pulmonary artery and its right and left main branches.

An electrocardiographic record was taken in seven cases. In six cases there was a high and pointed P wave (P-pulmonale), and a right ventricular preponderance. Depression of the S-T segment and an inversion of the T wave was seen in two cases. Auricular fibrillation was present in one case.

Cardiac catheterization was done in one case; a rise of pulmonary pressure was recorded, and the oxygen content of the blood from the right side of the heart and pulmonary artery was normal.

DIAGNOSIS

The diagnosis of bilharzial cor pulmonale in Egypt is usually suspected in patients that show signs of dilatation of the pulmonary artery with pulmonary hypertension and right ventricular enlargement in the presence of visceral bilharziasis. The diagnosis is supported when the characteristic roentgenographic and electrocardiographic changes are seen.

Cardiac catheterization is of help in differentiating bilharzial cor pulmonale from congenital cardiac malformations that produce a similar picture.

The differential diagnosis usually offers no difficulty except from the condition of atrial septal defect.

The latter is commoner in females than in males, and the patients are not necessarily subjects of somatic bilharziasis. Hilar dance is much more marked, and the peripheral pulmonary branches show marked pulsations, but lack the tortuous, beaded character seen in pulmonary bilharziasis. The aorta always shows marked hypoplasia. Cardiac catheterization shows no rise of pulmonary pressure except in the rare patients who develop pulmonary hypertension, and the oxygen saturation of the blood from the right side of the heart is always higher than that of the venous blood. The electrocardiogram shows a partial or complete right bundle branch block in the majority of cases.

SUMMARY

Pulmonary heart disease due to Bilharzia is a fairly common condition in hospital practice in Egypt. It has an incidence of 4 per cent among cardiac patients admitted to the free University Hospitals.

The underlying pathology is a process of repeated embolism of the pulmonary arterioles with either the *Schistosoma haematobium* or *mansoni* ova. Impaction

of the ova in the arterioles accompanying the respiratory bronchioles is followed by their escape into the perivascular tissues leading to a necrotizing arteriolitis.

The healing process that follows results in an obliterative arteriolitis, obstruction to the pulmonary blood flow, a rise of pulmonary pressure and ultimately a dilatation of the trunk and main branches of the pulmonary artery, and right ventricular hypertrophy.

The condition is commonly met with in male land laborers during the second, third, and fourth decades of life, and there is always a history of repeated infection with Bilharzia, either of the urinary or intestinal tracts or both. The heart becomes enlarged, mainly to the left, pulsations caused by enlargement of the right ventricle and dilatation of the pulmonary artery are often seen and felt to the left of the sternum, and a diastolic shock is usually felt in the second left intercostal space. The second sound in the pulmonary area is always accentuated and occasionally split. A harsh systolic murmur is heard in the pulmonary area in three-fourths of the cases, and a functional pulmonary regurgitant murmur (Graham Steell murmur) is heard in about one-third of the cases. Irregularities of rhythm are uncommon. Auricular fibrillation was met with in one out of twenty cases. Cyanosis is not a feature and is only met with in patients with cardiac failure. The lungs are always emphysematous.

Somatic bilharziasis is indicated by hepatic cirrhosis, the liver being either large or small, and by a large and firm spleen.

The x-ray picture is one of right ventricular hypertrophy and dilatation of the pulmonary trunk and its main branches. The peripheral pulmonary branches show a tortuous, beaded appearance, and perivascular mottling is seen in active cases.

Pulsations of the dilated pulmonary trunk and its branches are slight in contrast with those in cases of atrial septal defect, while calcification of these vessels has not been seen.

The electrocardiogram shows the characteristic P-pulmonale and a picture of right ventricular hypertrophy.

Cardiac catheterization was done in one case and revealed a rise of pulmonary pressure.

CASE REPORTS

CASE 1.—A.M.S., a male land laborer, 38 years old, was admitted to the hospital complaining of dyspnea on effort and a severe dry cough with an occasional hemoptysis. He gave a history of having been subject to repeated infection with urinary and intestinal bilharziasis for which he had been treated fourteen times over a period of eighteen years. There was no history of any other past illness.

Clinical examination revealed a slight venous congestion but no cyanosis or edema. Pulsations were visible in the third and fourth left intercostal spaces, and a diastolic shock was felt in the pulmonary area. A harsh systolic murmur was heard in the pulmonary area, and the second sound was markedly accentuated. Cardiac rhythm was regular. The systemic pressure was 110/70 mm. Hg. The chest was emphysematous. The lower margin of the liver was felt 3 fingerbreadths below the costal margin, and its anterior surface presented a fine irregularity. The spleen was felt one handbreadth below the left costal margin. The Wassermann reaction was negative, and the blood picture was normal. He had no evidence of urinary or intestinal parasitic infestation. The x-ray picture showed right ventricular hypertrophy as well as dilatation of the pulmonary artery and its main branches with clear lung fields. The basal pulmonary

branches showed a tortuous, beaded appearance, and fluoroscopy revealed no hilar dance. The electrocardiogram showed a gothic P-pulmonale and right ventricular hypertrophy with an elevation of the S-T segment in lead I and a depression of the same in the other leads.

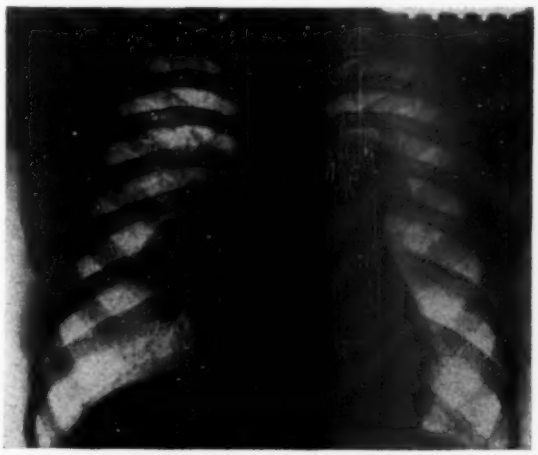
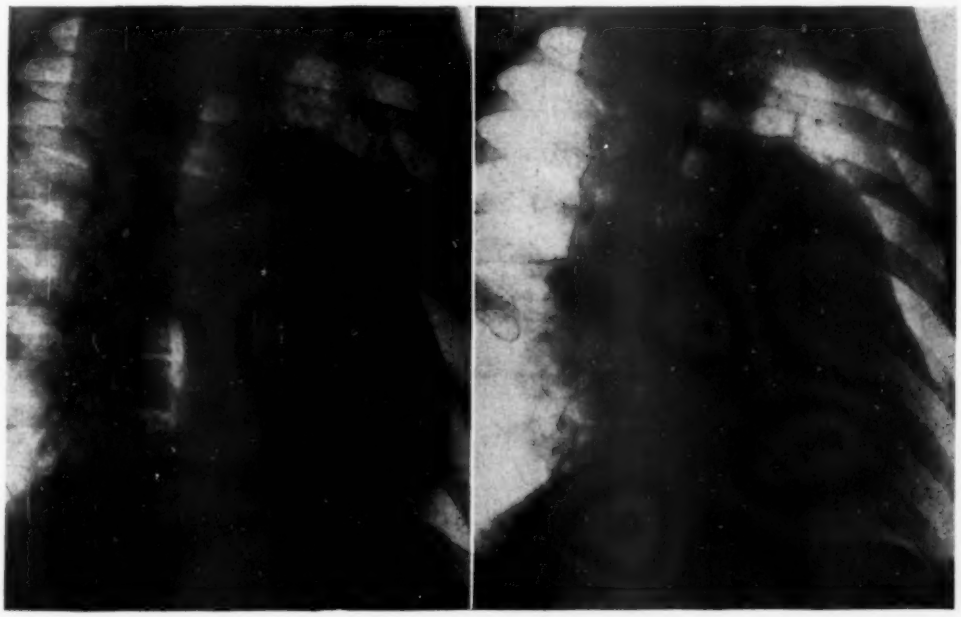


Fig. 1, *A* (Case 1).—Anteroposterior view showing enlargement of the right ventricle and dilatation of the pulmonary artery with an enlarged commalike right branch in the region of the hilum of the right lung. Two disklike opacities seen at the top of the right main branch are due to moderate-sized vessels seen in cross section. The peripheral pulmonary branches are more apparent than normal.



B. *C.*

Fig. 1, *B* and *C* (Case 1).—*B*, Right oblique view of the same patient showing the enlarged conus and pulmonary artery, broadening the upper part of the cardiac shadow. The dilated right main branch is shown coursing along from right to left with its shadow partly superimposed on that of the spine. *C*, Right oblique view with a barium swallow showing the impression caused by the right pulmonary artery displacing the right bronchus posteriorly. The aortic impression shows above. The left auricle has left no impression on the esophagus.

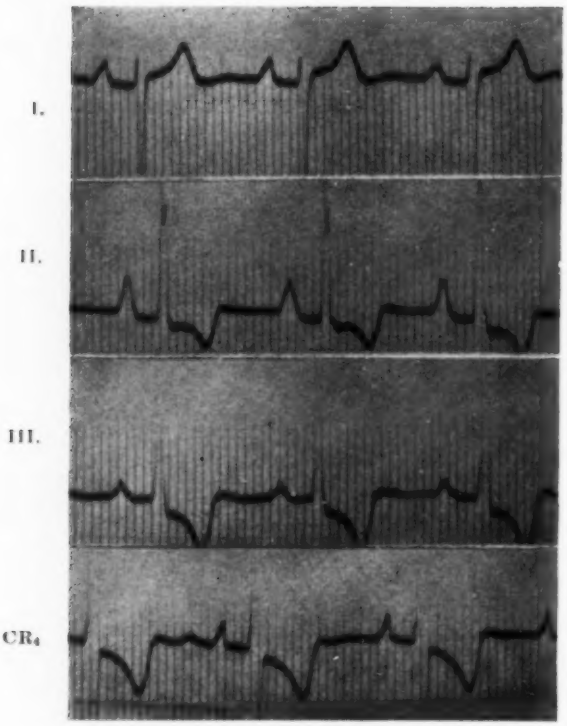


Fig. 1, *D* (Case 1).—Electrocardiographic record of the three standard leads and Lead CR_4 showing a P-pulmonale, right axis deviation, and right ventricular preponderance with depression of the S-T segment and T-wave inversion.

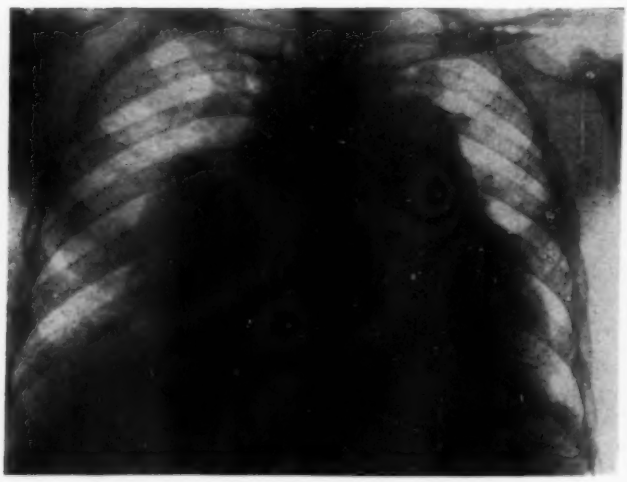


Fig. 2, *A*.

Fig. 2, *B*.

Fig. 2, *A* (Case 2).—Anteroposterior view showing marked cardiac enlargement. The left border is formed mainly by an enlarged right ventricle and a dilated pulmonary artery. The right border is formed by a big right auricle and the shadow of the right pulmonary artery and its branches.

Fig. 2, *B* (Case 2).—Right oblique view of the same patient with a barium-filled esophagus. There is no enlargement of the left auricle but only an impression due to the right pulmonary artery. Dilated branches of the latter are seen to the left of the picture.

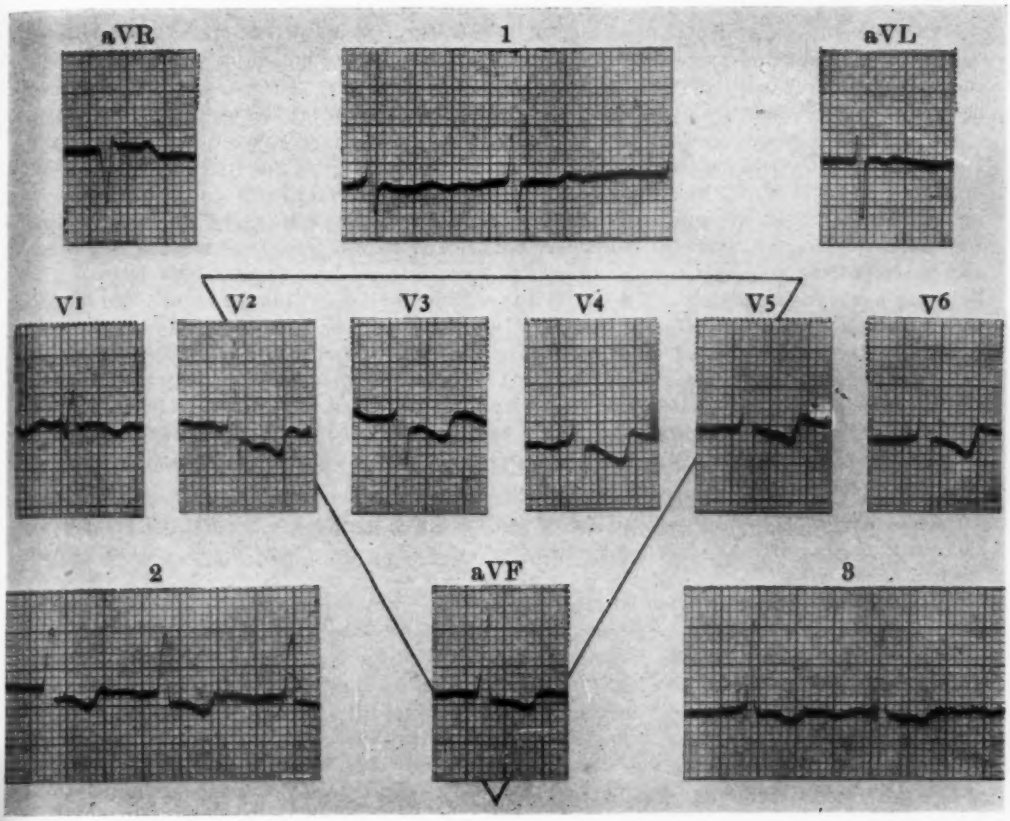


Fig. 2, *C* (Case 2).—Electrocardiographic record showing auricular fibrillation, right axis deviation, and right ventricular preponderance with S-T depression and inversion of the T wave.

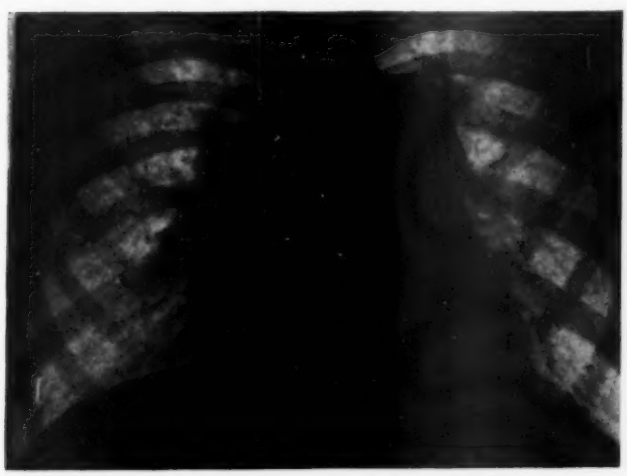


Fig. 3 (Case 3).—Anteroposterior view showing enlargement of the right ventricle and dilatation of the pulmonary artery and its branches. The smaller ones are irregular in outline, and several small nodules are seen along their course.

CASE 2.—M.A.S., a man 32 years old, was admitted to the hospital complaining of dyspnea on effort, dry cough, and edema of the legs. He had been short of breath for two years, but the edema had appeared only one month before he came to seek advice. He gave a history of having been treated three times for urinary and intestinal bilharziasis during the second decade of life.

Examination showed a moderately built man with a slight venous congestion in the neck and a little edema of the legs, but no cyanosis. The heart was moderately enlarged to the left, pulsations were seen and felt in the third, fourth, and fifth left intercostal spaces, and a diastolic shock was felt in the second left intercostal space. The heart was fibrillating, and the second sound was markedly accentuated in the pulmonary area. A systolic murmur was heard at the apex, and in the pulmonary area a systolic murmur and an early diastolic murmur were heard. The liver was moderately enlarged and firm and was slightly tender, and the spleen was also moderately enlarged. The chest was emphysematous, and râles could be heard over both bases.

The x-ray picture showed right ventricular hypertrophy and dilatation of the pulmonary artery and its branches. (Hilar pulsations could hardly be detected on fluoroscopy.) The blood picture was normal. The Wassermann reaction was negative, and the blood pressure was 120/85 mm. Hg. The electrocardiogram showed right ventricular hypertrophy and auricular fibrillation.

Cardiac catheterization showed a pulmonary artery pressure of 60 mm. Hg and no evidence of arteriovenous shunt.

CASE 3.—F.A.E., a male land laborer, 19 years old, was admitted to the hospital complaining of pain in the epigastrium after meals, attacks of giddiness, and symptoms of urinary and intestinal bilharziasis.

Clinical examination revealed no venous congestion, cyanosis, or edema. There was no cardiac enlargement. Pulsations were seen and felt in the third and fourth left intercostal spaces. Cardiac rhythm was regular, the second sound was markedly accentuated in the pulmonary area, and a harsh systolic murmur was heard in the same area. The chest was emphysematous, and a few rhonchi were heard over both bases. The liver was hard and nodular and could only be felt in the midline, 2 fingerbreadths below the xiphisternal junction. The spleen was firm and extended 4 fingerbreadths below the costal margin. The blood pressure was 100/70 mm. Hg. The Wassermann reaction was negative, and the blood picture showed slight anemia with moderate eosinophilia. The patient had urinary and intestinal bilharziasis.

The x-ray picture showed right ventricular enlargement and dilatation of the pulmonary vessels with the mottling of the lung fields that is often seen in active cases.

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Clinical Reports

BLASTOMYCOSIS WITH CARDIAC INVOLVEMENT AND PERIPHERAL EMBOLIZATION

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THE role of fungi in lesions of the endocardium has not received the emphasis that has been accorded other etiological agents. Even though fungi are not commonly the cause of such conditions, they should be suspected, especially in cases where the etiology is obscure. The correct diagnosis can help in the evaluation of both the prognosis and treatment. In a consideration of treatment, it is important to know whether the condition is caused by a fungus, since this may contraindicate the usual antibiotics used in bacterial diseases. Reports in the literature[1] suggest the possibility of the dissemination of a fungus infection by removal of the associated bacterial flora that normally inhibit the growth of the fungus. Included in the list of reported fungi causing endocardial lesions are those due to candida,[1-3] coccidioides,[4] aspergillus,[1] actinomyces,[5,6] and histoplasma.[6,7] In addition, a review of the literature reveals instances of cardiac involvement by *Blastomyces dermatitidis*, affecting not only the endocardium but also the myocardium and epicardium.[8-13] Many of these facts, which are usually not considered, were brought to our attention recently by an unusual case. This patient had an endocarditis caused by *B. dermatitidis* involving the left side of the heart with peripheral embolic phenomena.

CASE REPORT

The patient, a 33-year-old Negro man, was admitted to the University of Texas Hospitals on March 24, 1951. Two days prior to admission, while sawing a log, he experienced numbness of the low part of the back and flexor aspects of the lower extremities. Within two hours he developed severe aching pain in both legs extending down to the soles of the feet with extreme tenderness of the posterior portions of the lower extremities which was severe enough to prevent walking. There had been several episodes of vomiting since the onset of the pain, one mild bout of coughing which was productive of blood-streaked sputum, and a questionable history of fever. The only other features of note were a past history of gonorrhea in 1938, treatment for syphilis in 1948, and frontal headaches two months prior to the present illness for which he consulted a dentist and subsequently had several teeth extracted.

The physical examination on admission showed a regular pulse of 82 per minute, a temperature of 102.8° F., and a blood pressure of 146/84 mm. Hg. The lungs were clear to percussion and auscultation throughout, and examination of the heart revealed only a soft systolic murmur heard

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over the entire precordium. Extreme hyperesthesia of the entire lower extremities with severe pain in the posterior thighs was noted. The distal two-thirds of the right leg were cold, the dorsalis pedis artery pulsation was absent, and neither the ankle nor patellar reflexes could be elicited. The physical examination was otherwise noncontributory.

On admission, the hemoglobin was 10.9 Gm. per cent with 3.03 million erythrocytes per c.mm., and the total leucocyte count was 17,000 per c.mm. with 56 per cent neutrophils, 2 per cent myelocytes, 6 per cent stab forms, 12 per cent lymphocytes, 2 per cent basophils, 13 per cent eosinophils, and 9 per cent monocytes. A sickling preparation was negative, and the sedimentation rate was 36 mm. in one hour (Cutler). The admission urinalysis was normal, but eight to ten leucocytes and one to three erythrocytes per high-power field were noted on the eighth hospital day with clumps of leucocytes being noted on both the twelfth and fifteenth hospital days. Blood cultures on five separate days were without growth after twelve days on blood agar cultured at 37° C., and neither fungi nor acid-fast organisms were found on cultures of the sputum. An electrocardiogram on the third hospital day revealed a sinus tachycardia of 102 with slight right axis deviation. An increased transverse diameter of the heart, straightening of the left heart border, and clear lung fields were noted in the roentgenograms, and fluoroscopy revealed some right ventricular enlargement with prominence of the pulmonary segment. Abdominal films taken in the upright and supine positions on the twelfth day were consistent with an adynamic ileus. Bone surveys were negative. Intravenous urograms taken the day prior to death showed no concentration of the dye after one hour. The Kahn and Kolmer serology tests, urine bilirubin and urobilinogen, urine porphyrin (sunlight exclusion test), blood sugar, nonprotein nitrogen, serum chlorides, carbon-dioxide combining power, serum bilirubin, serum sodium and potassium, spinal fluid chemistries and cultures, agglutinations for typhoid, paratyphoid, brucella, and tularemia, skin tests for trichinosis, and a biopsy of the gastrocnemius muscle were negative or within normal limits.

Course in the Hospital.—The diagnosis most strongly considered was subacute bacterial endocarditis, and penicillin therapy was started with a dosage of 100,000 units every three hours after blood cultures were taken. During the first week, the hyperesthesia of the lower extremities diminished greatly, and the patient was able to move the legs, but hyperesthesia of the skin over the dorsum of the right foot persisted with the right great toe becoming progressively cyanotic. The dorsalis pedis artery and posterior tibial artery pulsations were never obtainable in the right leg, and the right Achilles tendon reflex was never elicited. Several lumbar sympathetic blocks were done, but neither subjective nor objective signs of improvement were noted. On the ninth day, the patient complained of dull aching pain in both upper quadrants of the abdomen which was followed in two days by similar pain in the right flank, but no signs of peritoneal irritation or bulging in the flanks could be detected. It was felt that the onset of the abdominal pain was due to embolic phenomena with involvement of the right kidney and other abdominal viscera. Terramycin, given orally and intravenously, was then started, and the temperature, which averaged about 103° F. during the first seven days in the hospital, diminished to normal for the last two days of life. Toward the end of the illness, the patient vomited dark brown material several times, and hemoptysis occurred during the terminal four days amounting to about a cup of slightly blood-streaked sputum. The systolic murmur became moderately loud and was consistently present with no diastolic component ever heard. Neither enlargement of the abdominal viscera nor peripheral petechial hemorrhages were ever detected. The anemia noted on admission became more severe in spite of transfusions of whole blood. It was thought that, with the return of the temperature to normal and the negative blood cultures, the patient was responding favorably to therapy, but on the afternoon of the fifteenth day, the pulse became weak, the blood pressure fell, and the respiratory rate rose to 36 with the patient becoming cold and sweaty. Death followed shortly.

Autopsy Findings.—At necropsy, which was done 41.5 hours after death, the body showed good development and appeared to be well nourished. External examination of the body revealed that the right great toe was gangrenous, but otherwise no lesions were noted on the skin or mucous membranes. When the chest was opened, 300 c.c. of straw-colored fluid were obtained from the left pleural space, 250 c.c. from the right pleural space, and 15 c.c. from the pericardial sac. When

the lower lobe of the left lung was cut, a tumor was noted in the upper medial portion which was continuous with a large tumor in the posterior mediastinum. This tumor, measuring 9 by 6.5 by 6 cm., also infiltrated through the pericardium and extended to completely destroy the left auricular appendage and invade through the full thickness of the left atrial wall where it appeared through the endocardial surface in the form of multiple nodules, the largest being hemorrhagic and measuring 1.5 cm. in diameter (Fig. 1). When the great vessels of the chest were dissected, some construction of the pulmonary veins was noted. The superior vena cava was infiltrated by the tumor which formed a papillary growth on the luminal surface measuring 3.5 by 1.5 cm. The main tumor was firm to palpation and cut with considerable difficulty, revealing a yellow-white surface appearing as connective tissue. The endocardial lesions were soft, the largest appearing as an organized thrombus.

Fig. 1.—Vegetative lesions on the endocardium of the left atrium.

Other than the tumor mentioned, the thoracic organs were without gross changes except for passive congestion of the lungs. When the abdomen was opened, 400 c.c of straw-colored fluid were noted. A large area of superficial hemorrhage on the anterior surface of the right psoas muscle and numerous large infarcts of the kidneys with thrombosis of several of the smaller renal vessels were the only gross findings noted on examination of the abdominal viscera including the genitals. An area of epidural hemorrhage was seen in the left middle cranial fossa.

Histological sections taken from the main tumor revealed a marked proliferation of fibrocollagenous tissue through which were scattered many areas of inflammatory reaction with a variable amount of necrosis containing lymphocytes, plasma cells, epithelioid cells, mononuclear and multinuclear giant cells, and organisms showing single budding forms which were histologically consistent with the spore stage of blastomyces. The most active lesions were in the nodules on the endocardial surface of the left atrium where, in one organized thrombus, the organisms were observed both in the spore and mycelial stages (Figs. 2 and 3). Multiple sections taken from the myocardium of all chambers of the heart showed many small areas of vascular thrombosis with surrounding inflammatory reaction and muscle destruction, with a few of these areas containing the spore stage of the fungus. Kidney sections showed large areas of infarction and thrombosis of the blood vessels with one large thrombus containing organisms both in the spore and mycelial stages. Inflammatory reactions with vascular thrombosis were noted in sections taken from the pancreas, right psoas muscle, the tissues around the right adrenal, and in one testicle, but the only organisms observed which were in the spore stage were found in the pancreas and psoas muscle. In spite of numerous sections, no lesions were noted in the spleen or liver. Sections taken from the cerebral meninges revealed one thrombus containing organisms in the mycelial and spore stages.

DISCUSSION

Among the possible etiological agents considered in this case following necropsy were *B. dermatitidis*, *Blastomyces brasiliensis*, and *Cryptococcus neoformans*. The authors feel that the organism is *B. dermatitidis* because *C. neoformans* does not form hyphae,[14] and *B. brasiliensis* characteristically undergoes multiple as well as singular budding in the spore stage,[14] whereas *B. dermatitidis* undergoes singular budding only in the spore stage and forms hyphae on growth below 37° C.[14,15] We believe the formation of hyphae in this case, seen only in blood thrombi, was due to growth of the organisms on what was essentially an unincubated blood culture during the 41.5 hours after death.

In considering the pathogenesis of the lesions, we agree with Baker[16] that the direct method of spread is important. In this case, the infection began in the left lower lobe of the lung and first spread through the pleura into the mediastinum, then through the pericardium into the heart. Invasion of the heart took place primarily through the left auricular appendage with extension through the full thickness of the heart wall and appearance of the inflammatory reaction on the endocardial surface, resulting in the formation of septic thrombi and, eventually, septic emboli causing the peripheral vascular phenomena noted.

On viewing the case in retrospect, it is felt that the proper diagnosis of the case might have been made clinically had there been a greater awareness that fungi can cause endocardial lesions.

In the therapy that this patient received, penicillin was of no apparent value when used during the early stages of the course when embolic phenomena were occurring, and terramycin used terminally cannot be adequately evaluated in spite of the apparent clinical improvement of the patient. It would seem that with our present knowledge of the use of antibiotics in such conditions, they are probably of little use and may actually have harmful effects by enhancing the virulence of the fungi.

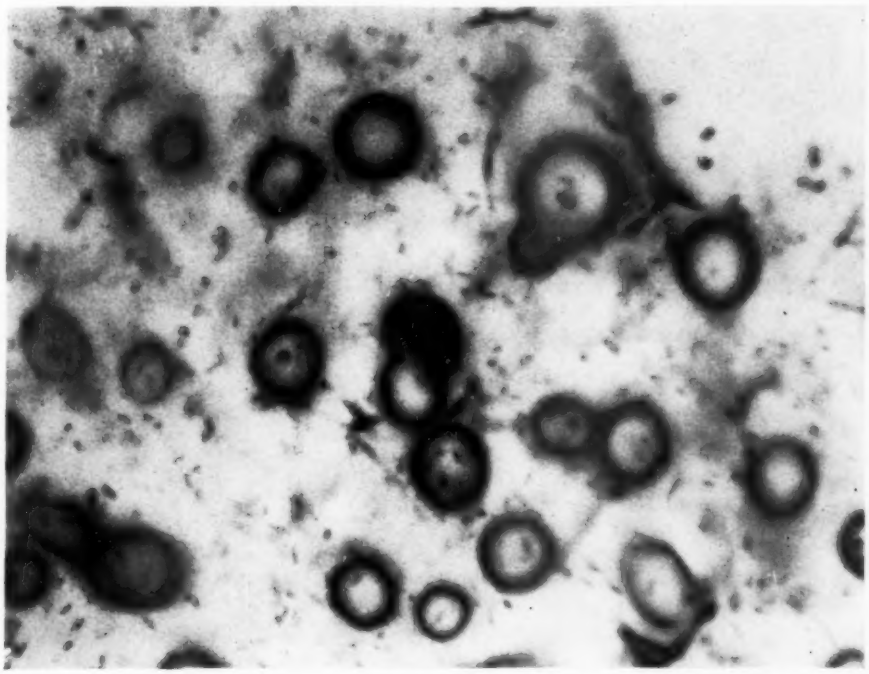

Fig. 2.—*Blastomyces dermatitidis* from vegetative lesion of the left atrial endocardium; spore form, 6 to 10 microns in diameter. (Stoughton stain, ×1,995.)

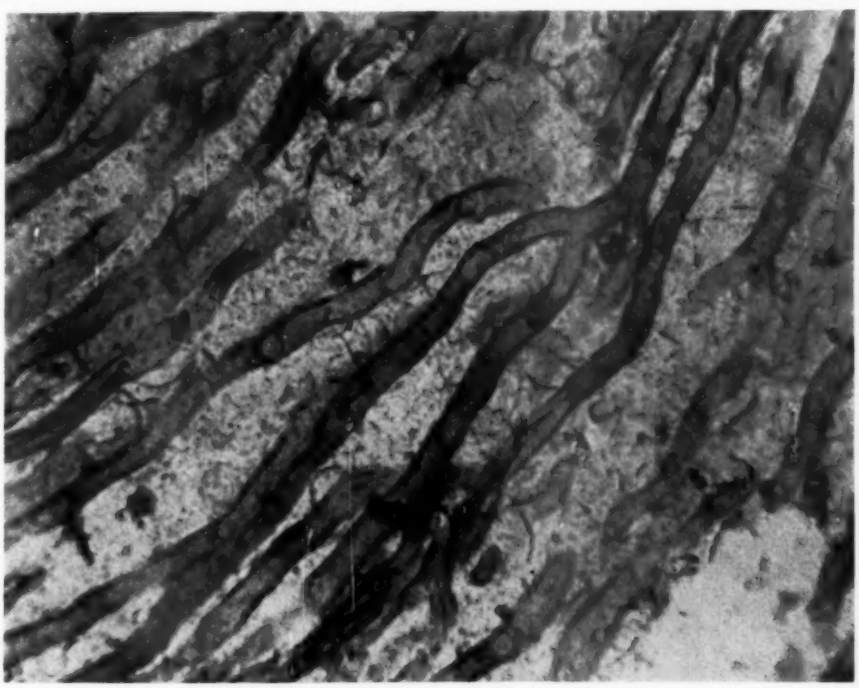

Fig. 3.—*Blastomyces dermatitidis* from vegetative lesion of the left atrial endocardium; mycelial form, 4 to 5 microns in diameter. (Stoughton stain, ×722.)

SUMMARY

A case of blastomycosis involving the left side of the heart with the production of peripheral embolic phenomena has been presented with a discussion of its pathogenesis. Brief mention was made of the role of other fungi in producing cardiac lesions and the possible harmful effects of antibiotics on such conditions.

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TRANSPOSITION OF THE AORTA AND LEVOPOSITION OF THE PULMONARY ARTERY

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IN 1949, Taussig and Bing[1] reported as a new clinical syndrome the correlated clinical, physiological, and pathological study of a case of congenital heart disease characterized by transposition of the aorta and levoposition of the pulmonary artery. While these authors stated that the existence of this anomaly was postulated by Pernkopf,[2] it seems actually to have been observed by Brown,[3] who, in 1939, wrote: "In other cases (of complete transposition) there is a defect of the interventricular septum. . . . The aorta arises anteriorly from the conus of the right ventricle while the pulmonary artery situated posteriorly may override the defect and thus arises from both ventricles." Since the description of Taussig and Bing, van Buchem, van Wermeskerken, and Orie,[4] in 1950, reported two cases under the title "Transposition of the Aorta (Taussig's Syndrome)." One of these was proved pathologically to be similar to that of Taussig and Bing, but in both there were important clinical and physiological differences from the syndrome as originally described. Campbell and Suzman,[5] in 1950, under the title "Transposition of the Aorta and Pulmonary Artery" reported twenty-three cases which were similar clinically to that of Taussig and Bing, but in none of the three of these investigated by angiocardiography was the one unique feature of the Taussig-Bing syndrome, namely a pulmonary artery which arises from the left ventricle and overrides the ventricular septal defect, definitely present. In fact, review of the published angiograms in this disease reveals none in which this point could be established with certainty during life. It seemed of interest, therefore, to report the present case in which angiocardiography clearly showed that not only did the aorta arise from the right ventricle, but that the pulmonary artery overrode the ventricular septal defect.

CASE REPORT

The patient was a 9-year-old schoolboy. He was born following a normal pregnancy, but he was cyanotic from birth and a heart murmur was heard at the age of 4 months. He was always small, underdeveloped, and somewhat backward in school. Exercise tolerance was fair, and

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Fig. 2.

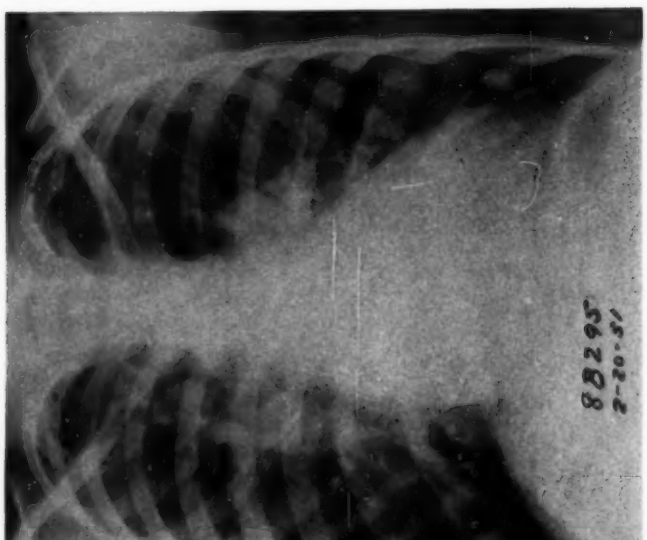

Fig. 1.

Fig. 1.—Anteroposterior roentgenogram of the chest showing increased vascularity of the lungs.

Fig. 2.—Roentgenogram taken in the left anterior oblique position one and one-half seconds after the injection of Diodrast. The aorta is shown arising from the right ventricle and the pulmonary artery arising from both ventricles and overriding the ventricular septum.

cyanosis was not made worse by exercise. Squatting, however, was frequently noted after exertion. He had frequent bouts of fever and collapse. Clinical study elsewhere resulted in the diagnosis of Eisenmenger's syndrome.

Physical Examination.—The patient was a small boy, weighing 46 pounds and having the physical characteristics of a child of 6 years. There was moderate cyanosis of the lips and nails, and clubbing of the fingers was present. No venous distention was apparent. The lungs were clear to physical examination. The heart was enlarged to the anterior axillary line. The pulmonary second sound was loud and booming. There was a Grade 2 systolic murmur best heard in the third intercostal space at the left sternal border. Rhythm was regular. Blood pressure was 80/60 mm. Hg. Liver, spleen, and kidneys were not felt. No edema was noted.

Laboratory Data.—Urinalysis revealed 1 plus proteinuria, but no other abnormality. There was a moderate polycythemia (hematocrit 58), but the blood was otherwise normal, including differential counts. Blood sugar, urea nitrogen, and total protein were within normal limits.

Electrocardiogram.—Standard and unipolar limb leads and unipolar chest leads were interpreted as showing right ventricular hypertrophy and incomplete right bundle branch block.

Roentgenogram.—Radiographic examination of the chest by plain film (Fig. 1) and fluoroscopy showed an enlarged heart with a marked increase in the size and prominence of the pulmonary vascular markings. There was expansile pulsation of the hilar vessels at fluoroscopy. The left border of the heart extended downward and to the left, suggesting left ventricular enlargement. The usual aortic projection to the left was absent.

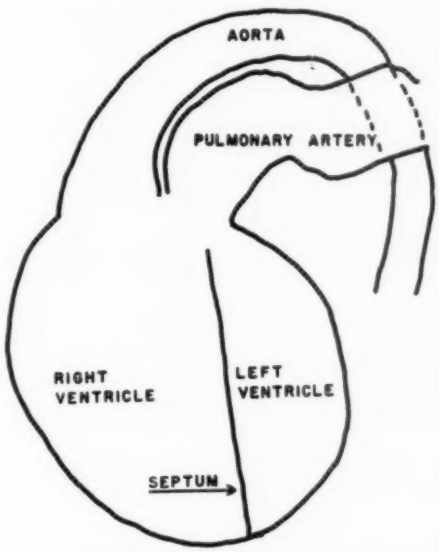

Fig. 3.—Diagram of Fig. 2.

Angiocardiography.—Angiocardiograms were made in the left anterior oblique position, 25 c.c. of 70 per cent Diodrast being used. The one-second film showed good filling of the right ventricle. At one and one-half seconds, the aorta was filled, the ascending portion being well anterior and apparently arising entirely from the right ventricle (Figs. 2 and 3). There was simultaneous filling of the pulmonary artery (best shown on the two-second film) which was situated directly above the ventricular septum, the lower two-thirds of which were well shown and quite straight. Subsequent films up to seven seconds showed poor filling of the left ventricle and apparent reopacification of the pulmonary artery, suggesting recirculation of Diodrast through the lungs.

Cardiac Catheterization.—The results of cardiac catheterization, which was performed by the standard technique in use in this laboratory,[6,7] are shown in Table I. The catheter was passed

from the right auricle through the right ventricle into the aorta and subsequently passed into the pulmonary artery by the same route. Blood from the pulmonary artery had a higher oxygen content than that in the aorta; hence the great vessels were transposed. The equality of systolic pressures in the right ventricle, aorta, and pulmonary artery is evidence for a ventricular septal defect, probably with overriding. Pulmonary blood flow was greatly increased, while peripheral blood flow was approximately normal.

TABLE I. RESULTS OF CARDIAC CATHETERIZATION

LOCATION	PRESSURE (MM. Hg)			OXYGEN	
	SYSTOLIC	DIASTOLIC	MEAN	CONTENT (VOL. %)	SATURATION (%)
Superior vena cava				13.8	58
Right auricle				14.3	60
			2	14.3	60
				13.8	58
Right ventricle	87	4			
Pulmonary artery	82	54	64	21.9	92
Aorta	88	58	68	18.9	79

Oxygen consumption	146 c.c. per minute
Aortic blood flow	3.0 L. per minute
Pulmonary blood flow	11.3 L. per minute
Shunts:	
Right ventricle to pulmonary artery	1.7 L. per minute
Left ventricle to aorta	1.7 L. per minute

DISCUSSION

The case of Bing and Taussig[1] and the series of Campbell and Suzman[5] bring into focus the problem of a cyanotic patient with increased pulmonary vascular markings (pulmonary "pleonemia") and at least a fair prognosis as to life expectancy. Other conditions associated with increased pulmonary blood flow, as atrial septal defect or patent ductus arteriosus, have cyanosis late if at all. Hence the cyanosis, the increased pulmonary blood flow, and at the same time oxygenation of the peripheral arterial blood sufficient to permit survival to early adult life are probably due to the mixing of systemic and pulmonary circuits in a common pressure chamber, the ventricle. Cyanosis with a highly vascularized lung is seen in individuals with a single ventricle, a single ventricle with transposition of the great vessels, a ventricular septal defect with transposition of the great vessels, a ventricular septal defect with an overriding aorta (Eisenmenger's syndrome), or a ventricular septal defect with a transposed aorta and an overriding pulmonary artery, the Taussig-Bing syndrome. From this group, the Eisenmenger syndrome can often be separated clinically by the tendency to the late development of cyanosis in this syndrome. Clear-cut differentiation of the other possibilities on clinical grounds alone is

not at present attainable, for Campbell and Suzman[5] have emphasized that the classic x-ray picture of transposition of the great vessels in infancy is not seen in this group.

Physiologic study of these patients by cardiac catheterization will separate the cases of transposition by the finding of a higher oxygen saturation in the pulmonary artery than in a peripheral artery. If the aorta can be entered with the catheter, the presence of a ventricular septal defect will be confirmed. Systolic pressures in the pulmonary artery, right ventricle, and aorta (or peripheral artery) should be approximately equal if there is a large ventricular septal defect with overriding. In this respect, the two cases of van Buchem, van Wermeskerken, and Orie[4] are unique in that a coexistent pulmonic stenosis was considered to be present, and both failed to show a prominent pulmonary artery or signs of increased vascularity of the lungs.

It is only by angiocardiography that the unique feature of the Taussig-Bing syndrome, a pulmonary artery overriding a ventricular septal defect, can be demonstrated during life. As their patient died after three injections of Diodrast during this procedure, Taussig and Bing warned against its use. In six subsequent cases of this or a closely similar anomaly, including the present one, no ill effects followed the injection of radiopaque material.

Obviously this anomaly can be present with an angiocardiogram that is indistinguishable from that of transposition of the aorta with ventricular septal defect but without overriding of the pulmonary artery. Demonstration of the overriding of the pulmonary artery will be accomplished only when the septum and the pulmonary artery are visualized, as in the case reported here.

SUMMARY

1. A case of the Taussig-Bing syndrome (transposition of the aorta with levoposition of the pulmonary artery) definitely diagnosed in life is reported.

2. From a review of the literature, it is concluded that this syndrome can be separated from transposition of the great vessels with ventricular septal defect only by angiocardiography and then only in favorable circumstances.

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SECOND-DEGREE HEART BLOCK AND WENCKEBACH PHENOMENON ASSOCIATED WITH ANXIETY

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SECOND-DEGREE auriculoventricular heart block with Wenckebach periods is apparently rare in patients without organic heart disease or drug intoxication. A review of the literature reveals only five well-documented cases. In none of these has the arrhythmia been described as a concomitant of anxiety. Altschule's[1] recent summary of the effects of emotion upon the circulation implies that only minor degrees of heart block are seen in physically healthy but emotionally disturbed individuals. Since our patient, a man without demonstrable organic disease, exhibited major cardiac conduction abnormalities during two anxiety attacks, these observations seem worth reporting.

CASE REPORT

The patient, a 27-year-old, married, Negro, graduate student in physiology, was seen in the Emergency Room of the George Washington University Hospital on the evening of Dec. 19, 1949, complaining of bouts of smothering with dizziness, palpitations, sweating, and chest pain of one week's duration. Although recent studies elsewhere had reported the absence of organic disease, he presented himself as a cardiac patient "in order to get prompt attention." Further history revealed that the symptoms had started in the following manner. One week prior to admission he had been studying the coronary circulation and its abnormalities and that evening had suddenly developed the first attack. He became extremely agitated, feared that he had fatal coronary artery disease, and was reminded of a friendly professor whose sudden death he had witnessed the year before. Immediately thereafter he was admitted to the hospital associated with his school where it was found that the blood pressure was elevated with the attack. No other abnormalities were detected, and pharmacologic studies for pheochromocytoma were reported to have been negative. Since then similar episodes had occurred. The past and family histories were noncontributory. To his knowledge he had never had rheumatic fever, a heart murmur, or an elevated blood pressure.

Examination in the Emergency Room of the George Washington University Hospital revealed a blood pressure of 170/100 mm. Hg, a pulse of 60 with "occasional dropped beats," and no other abnormalities. He was hospitalized for further study and psychiatric evaluation. When seen shortly thereafter, he was found to be a well-developed, well-nourished, young Negro man who was tense and anxious. The blood pressure had fallen to 140/90 mm. Hg. The heart rate was 60, and the rhythm was now regular. Examination was otherwise negative except for dermatographia and cool perspiring hands and feet. On subsequent occasions the blood pressure showed considerable lability. During an anxiety attack the pressure rose to 150/80 mm. Hg; during an amytal sedation test it dropped to 90/55 mm. Hg; and during the last three days of his hospital stay, when he was more relaxed, it stabilized in the neighborhood of 115/70 mm. Hg. The fundi

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were negative. Cardiovascular examination and heart roentgenograms were normal as were the blood count, urinalysis, sedimentation rate, urine concentration test, blood urea nitrogen, and serologic tests. Retrograde and intravenous pyelograms done elsewhere were reportedly normal.

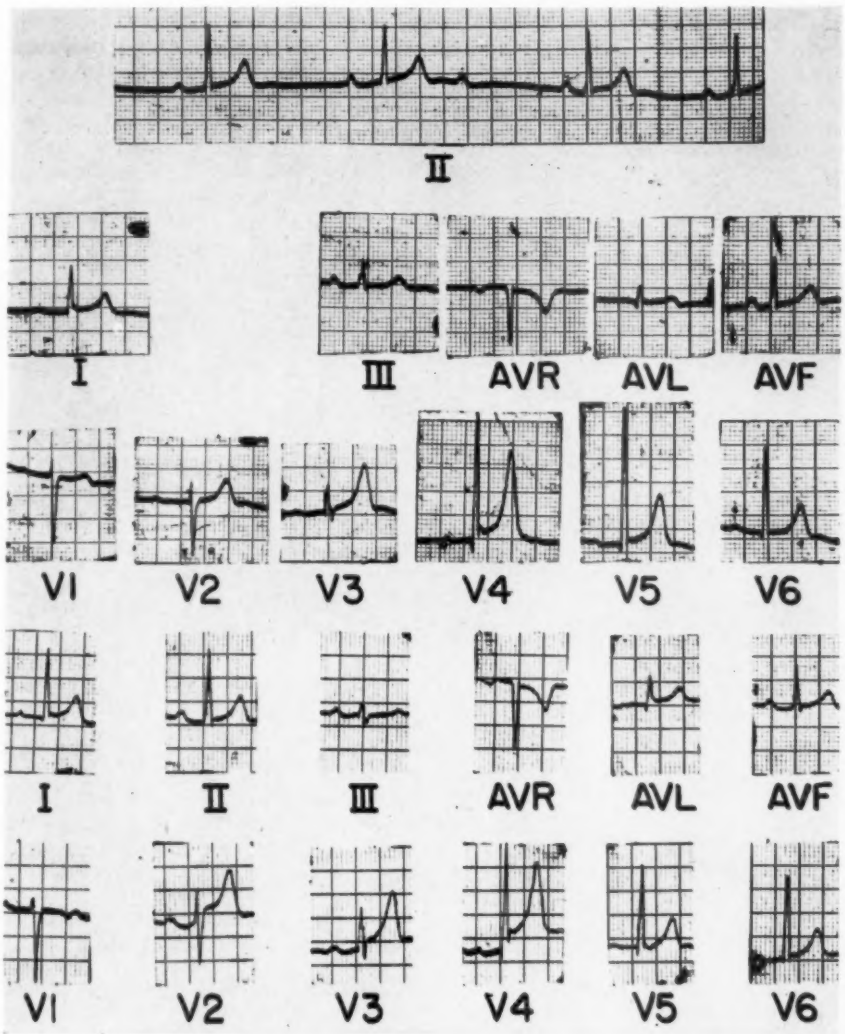

Fig. 1.—*A*, Admission tracing taken on Dec. 21, 1949. The top row shows the Wenckebach phenomenon in Lead II. *B*, Follow-up tracing taken July 17, 1951, showing prolonged P-R interval of 0.24 second. V_5 was incorrectly standardized at 4 mm. instead of 1 cm.

On the day after admission the patient was seen during one of the attacks. At this time the blood pressure was 150/80 mm. Hg. The twelve-lead electrocardiogram (Fig. 1,*A*) showed an auricular rate of 54 and a ventricular rate of 50; the P-R interval varied between 0.19 and 0.30 second, dropped ventricular beats were irregularly present, and the Wenckebach phenomenon occurred in relation to these. The P waves were varying in configuration. The electrocardiogram was otherwise normal except for unusually high T waves, particularly in Leads V_3 and V_4. Subsequent tracings failed to show the arrhythmia, but it was presumably present in the Emergency Room where the intern had noted "occasional dropped beats." The patient was restudied electro-

cardiographically on a number of occasions during the five-day hospitalization. The T waves continued to be high but were less elevated than in the first tracing. Slight first-degree heart block of 0.21 to 0.24 second was found in all but one tracing, where the P-R interval was 0.19 second. An electrocardiogram (Fig. 2) in the standing position showed an increase in rate from 80 to 110 and a decrease in the P-R interval from 0.22 to 0.16 second. Hyperventilation was followed by no significant change. The administration of 250 mg. of tetraethyl ammonium chloride intravenously increased the rate from 70 to 100 and shortened the P-R interval from 0.23 to 0.18 second. Fifteen minutes after the subcutaneous injection of 0.3 mg. of Prostigmine, the rate decreased from 80 to 72; the P-R interval increased from 0.22 to 0.24 second.

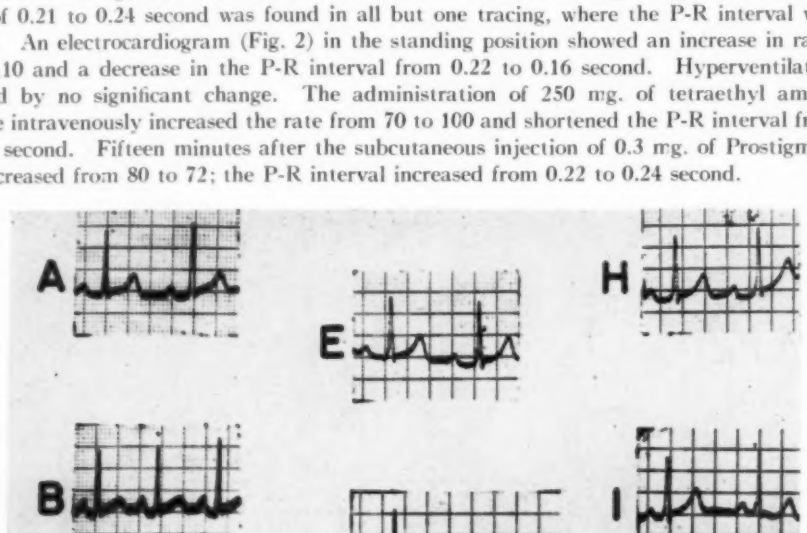

Fig. 2.—Lead II has been used throughout. *A*, Control, Dec. 21, 1949. The rate was 80, the P-R interval 0.22 second. *B*, In the standing position the rate was 110, the P-R interval 0.16 second. *C*, Fifteen minutes after 0.3 mg. of Prostigmine subcutaneously, the rate was 72, the P-R interval 0.24 second. *D*, Immediately after 250 mg. of tetraethyl ammonium chloride intravenously, the rate was 100, the P-R interval 0.18 second. *E*, Control, July 17, 1951. The rate was 74, the P-R interval 0.24 second. *F*, When the breath was held in deep inspiration, the rate was 57, the P-R interval 0.25 to 0.27 second. *G*, On left carotid sinus pressure the rate was 61, the P-R interval 0.26 to 0.27 second. *H*, Control, July 17, 1951. The rate was 75, the P-R interval 0.24 second. *I*, Immediately after 0.8 mg. of atropine intravenously, the rate was 75, the P-R interval 0.16 second. *J*, Five minutes after atropine, the rate was 80, the P-R interval 0.18 to 0.19 second. *K*, Twenty-five minutes after atropine, the rate was 90, the P-R interval 0.20 second.

During the period in which the patient was undergoing medical study he was seen in five therapeutically oriented psychiatric interviews.* In these sessions it was learned that he was the second oldest of seven siblings. He had been an unusually sensitive and "good" boy though given to attacks of temper tantrums. His parents were divorced when he was in elementary

*By Dr. E. Prunier.

school, and his mother remarried while he was in college. He had reacted adversely to both of these events. The patient showed considerable ambivalence toward his father who was a chronic alcoholic. He had repressed feelings of dependency and hostility toward his mother. The latter were close enough to the surface for him to become dimly aware of them during the course of the interviews. When he realized that one of the attacks was precipitated by his mother's entry into the room, he impulsively asked her to step outside and then burst into sobs. Our information in regard to his relationship with his wife is inadequate. For financial reasons they lived in widely separated cities during most of the year, while their children were quartered in yet another town with his in-laws. Talking of his wife brought on a number of attacks. We also suspected that the patient might have sexual conflicts. He seemed unwilling to discuss this subject but stated that he was refraining from intercourse during his vacation visit with his wife, whom he had not seen for a number of months, for fear that it might injure him in his present condition. The final psychiatric impression was that the patient was suffering from anxiety hysteria and that the symptoms were related to repressed hostility which was sufficiently close to awareness to be causing much anxiety. It was inferred that guilt and self-punishment accompanied the repressed effect in view of the intense fear of death which he experienced during the attacks and at the thought of anything connected with death. In addition, there appeared to be unsolved dependency and sexual problems.

After the studies were completed, the patient was repeatedly reassured in regard to his physical condition. It appeared that he was now more willing to entertain the possibility that the symptoms were psychogenic, and he promised to seek further psychiatric aid when he returned to school.

He was seen briefly one and one-half years later in a follow-up examination. He stated that the symptoms had persisted for about three weeks after he returned to school and that the mere sight of an exposed heart in the experimental animal had been sufficient to bring them on. Rather than seek further psychiatric help, however, he "had taken the doctor's advice" and obtained as much rest and relaxation as possible. On this regimen the symptoms had disappeared without recurrence, and thoughts of possible heart trouble no longer distressed him. His wife was now living closer to him, and he was able to see her more frequently. He had undergone a number of medical checkups in the interim, and no abnormalities had been found. The blood pressure had stabilized at 110/70 mm. Hg.

On examination he still appeared tense, apprehensive, and guarded. The heart findings were normal; no murmurs were heard. The blood pressure was 120/80 mm. Hg and the pulse 75 and regular. A series of electrocardiograms was taken (Fig. 1,*B*, and Fig. 2). These showed a P-R interval of 0.24 second and relatively high T waves in the leads across the mid-chest. Breath holding in deep inspiration slowed the heart rate to 57 and lengthened the P-R interval to 0.25 to 0.27 second. The effect of eyeball pressure could not be determined because the patient could not tolerate the pain. Right carotid sinus pressure failed to change the heart rate or the duration of atrioventricular conduction; left carotid sinus pressure slowed the rate from 72 to 61 and increased the P-R interval from 0.24 to 0.27 second. Intravenous atropine (0.8 mg.) produced bizarre results. Immediately after its injection, and presumably before the drug had taken effect, the patient became anxious, writhed on the table, and exhibited irregular, spasmodic breathing. The heart rate showed no change, while the P-R interval shortened from 0.24 to 0.16 second. The blood pressure was 120/85 mm. Hg. It was obvious to the observer that the injection had made the patient extremely anxious. He was reassured successfully, and five minutes after injection the heart rate had increased to 80 and the P-R interval to 0.18 to 0.19 second. Fifteen minutes after the injection the patient complained of a dry mouth. The heart rate was 87 and the P-R interval 0.18 second. Twenty-five and thirty minutes following injection the rate was 95 to 90 and the P-R interval 0.20 to 0.19 second. Thus, it appeared that emotion had a greater influence on the auriculoventricular conduction time than the partial vagal inhibition produced by atropine.

DISCUSSION

We believe this patient's primary disturbance was emotional. While his neurosis was decompensated, he suffered from the attacks which were his presenting complaint. We found no evidence of organic disease to account for the attacks

TABLE I. REPORTED CASES OF SECOND-DEGREE HEART BLOCK IN PATIENTS WITH NORMAL HEARTS

AUTHORS	AGE, SEX, RACE	DEGREE OF BLOCK	SITTING OR STANDING	EXERCISE	ATROPINE	BREATH HOLDING	CAROTID SINUS AND EYEBALL PRESSURE	OTHER SIGNS OF AUTONOMIC IMBALANCE	EMOTIONAL FACTORS
Benedict and Evans	27 Male Negro	Transient first and second-degree block with W.P.; P-R prolonged to 0.23 on other occasions	P-R 0.16; rate increased to 110		See text	Inspiration: rate decreased from 75 to 57; P-R increased to 0.27	Left C.S.: rate from 72 to 61, P-R from 0.24 to 0.27; right C.S.: no effect	Dermatographia, cold sweating hands and feet, labile blood pressure	Anxiety hysteria with acute anxiety attacks
Donner and Merlen[8]	20 Male White	First and second-degree block with transient W.P.; P-R 0.21 to 0.25	Intermittent W.P.	W.P. disappeared	P-R dec. to 0.18, W.P. disappeared		E.P.: W.P. accentuated	Marked sweats, nausea, syncope, and dizziness	Not mentioned
Germain and Marty[9]	18 Male White	Dropped beats with ventricular escape; P-R 0.14 to 0.18					E.P.: slowed rate to 45, P waves disappeared, QRS normal		Occurred during draft exam.; absent next day
Laubry and associates[10]	11 Male White	First and second-degree block with transient W.P.	P-R 0.14; W.P. disappeared	W.P. disappeared	W.P. disappeared	Forced expiration: accentuated W.P.	C.S. and E.P.: accentuated W.P.	Not mentioned	Not mentioned
Levy[11]	14 Male White	First and second-degree block; P-R 0.26 to 0.30; occasional dropped beats		P-R 0.18; dropped beats absent	P-R 0.17 to 0.18. No dropped beats	Inspiration: dropped beats with W.P.	Right C.S.: 1 dropped beat with W.P., P-R 0.16 to 0.24; left C.S.: P-R 0.27, no dropped beats	Episodes of syncope	Not mentioned
Holmes and Weill[12]	22 Male White	First and second-degree block with W.P.; P-R 0.16 to 0.36	P-R 0.20; W.P. and second-degree block disappeared	Mild, no effect; vigorous normal P-R; W.P. disappeared	P-R 0.16 second-degree block and W.P. disappeared		No effect	Not mentioned	Not mentioned

Abbreviations: W.P. = Wenckebach phenomenon.
E.P. = eyeball pressure.
C.S. = carotid sinus pressure.

or the physical changes which accompanied them. It is known that transient hypertension may be emotionally induced. The arrhythmia may have been secondary to increased vagal tone, although our attempts at artificial stimulation and depression of vagal activity were inconclusive when measured by the changes produced in the P-R interval. While P-R changes did occur in the expected directions, they were not striking and were accompanied by considerable alterations in the cardiac rate. The bizarre results accompanying the intravenous injection of atropine were interesting chiefly because they illustrate the sensitivity of atrioventricular conduction to emotional stimuli in this patient. The changes occurred so rapidly after injection that one can assume that a neurogenic sympathomimetic mechanism was operating in their production. Consequently, the patient demonstrated both an increase and decrease in the conduction time following emotional stimuli.

When the patient was seen one and one-half years later the first-degree heart block was still present. This might be considered a variant of normal in view of the findings of Graybiel and colleagues[2] who reported this abnormality in 1.6 per cent of 1,000 healthy young aviators studied electrocardiographically. On the other hand, we might postulate that the prolonged conduction was secondary to the continued existence of increased vagal tone. Although the patient's neurosis was compensated at the follow-up examination, it continued to be present and might still have influenced the autonomic nervous system. First-degree heart block may be more frequent in persons with emotional difficulties. Of the 100 patients with prolonged P-R interval described by Logue and Hanson,[3] seven had neurocirculatory asthenia, and in nineteen no disease was found. In this latter group were four patients with psychiatric conditions and one with duodenal ulcer. In other words at least 11 per cent of their patients had psychological difficulties. Heyer and associates[4] found atrioventricular conduction time greater than 0.20 second in 3 per cent of 200 patients with mental disease, whereas this abnormality was present in only 0.5 per cent of their control group. Meyer and Billmann[5] reported this condition in four of 100 psychotic patients, while Logue, Hanson, and Knight[6] found it to be present in 4.7 per cent of 150 patients with neurocirculatory asthenia.

Although first- and second-degree heart block with Wenckebach periods has not been previously described as a cardiac manifestation of anxiety, we doubt that our case is unique. Friedman[7] has shown that cardiac arrhythmias are not infrequent during the acute anxiety attacks of neurocirculatory asthenia. They are likely to go unnoticed unless an electrocardiogram is taken during the attack as was done in our case. On reviewing the literature, we were able to find five well-documented reports[8-12] of second-degree heart block with the Wenckebach phenomenon in individuals with normal hearts and without drug intoxication. Certain observations on these and on our own patient are summarized in Table I. In addition, Sabathie and Gaspary[13] stated that they have followed four normal young patients with second-degree heart block for a period of two to fifteen years with no evidence of organic heart disease appearing during this interval. A review of the table shows that all the reported patients have been young men.

C.S. = carotid sinus pressure.

The heart block disappeared on standing, after exercise, and after atropine when these procedures were carried out. Breath holding in deep inspiration or expiration and carotid sinus and eyeball pressure tended to increase the block in most instances. Consequently, most authors have ascribed the phenomenon to increased vagal activity. As already stated, our attempts to corroborate this theory, as far as the patient's first-degree block was concerned, were suggestive but inconclusive. The effects of these procedures on the second-degree block could not be evaluated since the patient only exhibited this arrhythmia on two brief occasions while under observation.

A psychiatric history was not given, and presumably not taken, in any of the tabulated cases. Whether emotional factors were of significance in any of these patients cannot therefore be evaluated. Their operation is suggested in the young man described by Germain and Marty,[9] where the arrhythmia was present during a period of stress, a draft examination, and absent the following day. The patient of Donner and Merlen,[8] complained of sweats, nausea before meals, dizziness, and several episodes of syncope, symptoms which may have been psychosomatic in origin.

Reports of other types of atrioventricular block in emotionally unstable but physically healthy persons are scattered through the literature. Among them are the studies of Marzahn,[14] Stein,[15] and Silverman and Goodman.[16] The first describes the occurrence of sinoauricular block in a 32-year-old white man who developed the classical symptoms of a cardiac neurosis following the death of a fellow worker in a crane accident for which the patient felt himself responsible. The second report concerns a 19-year-old Mexican boy, with marked emotional instability, who was found to have complete heart block in the supine position and marked first-degree block in the upright posture. Silverman and Goodman describe a 49-year-old Army sergeant with neurocirculatory asthenia in whom the P-R interval varied between 0.32 and 0.72 second. The atrioventricular conduction time shifted in parallel with the emotional state and was longest when the patient was most anxious and shorter when he was more relaxed. These patients illustrate that emotional factors may be involved in a variety of atrioventricular conduction disturbances which, although rare, may be observed more frequently in the future in view of the increasing interest in psychosomatic correlations.

SUMMARY

The transitory occurrence of first- and second-degree heart block with Wenckebach periods has been described in a 27-year-old Negro man without evidence of organic disease. Emotional factors, possibly mediated through the vagus nerve, are believed to have induced the arrhythmia. The literature on this subject has been reviewed.

The authors wish to acknowledge with gratitude the assistance of Dr. Edward L. Rea.

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Review of Recent Advances

THE SIGNIFICANCE OF THE ELECTROCARDIOGRAM IN ELECTROLYTE DISTURBANCES

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VARIATIONS in the blood levels of potassium, calcium, and occasionally magnesium are said to produce alterations in the electrocardiogram which may be helpful in the recognition of abnormal states.

The growing tendency to rely upon the electrocardiogram in the diagnosis of electrolyte disturbances in man makes a survey of our present knowledge in this area seem timely.

Magnesium usually produces no diagnostic alterations in man, although minor variations are seen.[1] Elevation of the blood *calcium* level increases the P-R and Q-T intervals, but the changes are too small to be useful.[2] Hypocalcemia produces prolongation of the S-T interval without affecting the T wave.[3-5] The change is not common and is often seen in other conditions. It occasionally may help to confirm a clinical suspicion. The only area in which the electrocardiogram may be of great value is that of potassium disturbances in the body, and most of this paper will be concerned with potassium.

The significance of the electrocardiogram in potassium disturbances is a controversial subject. As early as 1839,[6] an effect of potassium intoxication upon the heart was recognized. In 1883, Ringer[7] reported adverse effects from either deficiency or excess of potassium. Since 1937, a number of reports have compared the blood level of potassium with the electrocardiographic changes.[8-12] Many have pointed out the lack of exact correlation between the two, but yet have emphasized the rough parallel between them.

If we are to get the maximum information from the electrocardiogram in potassium disturbances, the following questions need to be answered if possible:

1. Does the electrocardiogram always reflect the blood level or direction of abnormality?
2. If not, how often are they parallel, and at what blood levels do significant electrocardiographic changes occur most frequently?
3. If at variance with the blood potassium concentration, what states do the electrocardiographic findings represent?
4. In what conditions is the electrocardiogram most reliable as an indicator of potassium deficiency or potassium excess?

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Not all of these questions can be answered now, but a consideration of them should clarify the role of the electrocardiogram in the diagnosis of potassium disturbances in the body.

THE ELECTROCARDIOGRAM AND THE SERUM CONCENTRATION OF POTASSIUM

Most investigators agree that the exact blood level of potassium is not reflected in the electrocardiogram. However, until 1938, when Winkler and associates[11] first discredited the idea, students believed that certain changes in the electrocardiogram always represented accurately the direction of serious abnormalities of potassium concentration in the body. Bellet and associates[14] studied a group of thirty-five patients with diabetic acidosis. Twenty-five of these showed hyperpotassemia before fluid therapy, and the electrocardiogram exhibited high peaked T waves with slight widening of the QRS complexes.[15-17] Marked prolongation of the P-R interval and diminution in the amplitude of the P wave often occur.[18] In severe cases the QRS becomes widened and may absorb the Q-T interval. The other ten had hypopotassemia when first seen. Seventy-nine patients with hypopotassemia from various causes all had some electrocardiographic alteration(s). The changes are given in detail because they represent an excellent description of the electrocardiographic findings of hypopotassemia. Only two had renal disease; this may explain the high degree of correlation between the electrocardiogram and the blood level in their series since it is in renal disease with multivaried electrolyte abnormalities that the blood potassium is most frequently at variance with the electrocardiographic changes. Thirty-three had a prolonged Q-T interval and a depressed S-T segment, the degree of change corresponding roughly to the severity of the hypopotassemia. Thirty-one had abnormal T waves and Q-T prolongation frequently followed by a U wave. The T-wave variation usually consisted of (1) slightly elevated initial S-T with late inversion, (2) inversion below the isoelectric line, and (3) isoelectric T waves. Six patients had an upright T wave of varying amplitude with a prolonged Q-T interval which was completely occupied by the T wave. Five patients had a low T wave not well demarcated from a pronounced U wave. Two patients had a normal T and normal Q-T interval followed by a very prominent U wave. Fifty-three per cent of the patients had definite U waves. There was a high degree of correlation between the extent of prolongation of the Q-T interval (corrected for rate)[19] and the level of the serum potassium.[20-22] These electrocardiographic abnormalities returned to normal as the blood potassium became normal, but quickly reverted to the hypopotassemic patterns when potassium administration was discontinued. The authors attributed the relapse to a shift into the cell, loss from the urine, and/or metabolic utilization. Critical evaluation of the individual case in this study is not possible since individual potassium concentrations are not tabulated. McAllen[22] stated that the prolonged T wave in hypopotassemia is really produced by a combined T-U wave. This is certainly true in some cases but not in all, as one can see from Bellet's studies.[14]

The Blood Level and the Electrocardiogram.—Others have failed to find the close relationship between the blood level of potassium and the electrocardiogram

which Bellet represented.[13,23] It is true, however, that the pattern of hyperpotassemia is far more reliable than that of hypopotassemia. Changes of hyperpotassemia occur frequently with blood levels above 6.8 to 7.6 and quite consistently with levels above 7.8 meq. per liter.[11] They may be normalized with sodium chloride administration alone.[15] However, the pattern may occur with a normal blood potassium, and Logue and Hurst[24] found it in one patient with a very low potassium concentration of 1.8 meq. per liter. Furthermore, the total potassium content of this patient's skeletal muscle was low.[25] The typical high, peaked T waves may be seen in myocardial infarction without hyperpotassemia which further discredits the specificity of the picture. However, the electrocardiographic changes in myocardial infarction have been suggested as due to shifts of potassium from within the cell to the outside.[26]

The pattern of hypopotassemia is even less specific, and most of the alterations may be seen in many other conditions. In addition to this, patients with low blood levels may present no electrocardiographic abnormality.[23] The author has seen a normal electrocardiogram in a uremic patient with a blood potassium of only 2 meq. per liter. In diabetic acidosis[14] and family periodic paralysis,[27] the electrocardiogram is fairly reliable as an indicator of hypokalemia. In uremia, where other electrolyte anomalies are present, the electrocardiogram is often misleading, especially if the patient has had therapy. Investigators estimate that 80 per cent of patients with various diseases with a blood potassium below 3.5 meq. per liter will show suggestive electrocardiographic aberrations while an even higher percentage of those with blood levels below 3.0 meq. per liter will demonstrate changes.

WHAT PRODUCES THE PATTERNS?

The rather considerable number of cases in which there is a lack of correlation between the blood concentration of potassium and the electrocardiographic changes indicates that the blood concentration of potassium is not the fundamental cause of the alterations. Currens and Crawford[23] showed this clearly in a series of patients. One of these who was treated for hypopotassemia received potassium chloride in one cubital vein, and blood was removed from the other for blood determinations. Simultaneous electrocardiographic tracings showed a hypopotassemic pattern when the blood potassium concentration was raised to 12.7 meq. per liter by the infusion. The electrocardiogram of another of his patients had normal T waves with a blood potassium concentration varying from 0.9 to 1.3 meq. per liter.

Neither does the intracellular potassium concentration seem to correspond to the electrocardiographic anomalies. Employing the best methods available at present for measurement of intracellular electrolytes, Crismon and associates[28] were unable to correlate the two in animals. Fitzhugh and Doyle[29] in this laboratory made similar observations.

Bryant[18] suggested that prolonged restriction of sodium can produce an effect on the electrocardiogram similar to that of elevation of the blood potassium. However, he did not conclude that the mechanisms of the effects are related.

Fitzhugh and Doyle[29] were able to reverse the electrocardiographic signs of potassium intoxication abruptly by administration of concentrated sodium chloride without changing the blood potassium concentration. These findings suggest that the relative concentration of electrolytes in the extracellular fluid may be of importance in the production of the electrocardiographic aberrations. One cannot rule out a shift in intracellular water with a change in intracellular potassium concentration as a cause of the electrocardiographic aberrations. Another factor might be the relative concentration of the extracellular fluid potassium versus that of the intracellular fluid, and some feel that anything which interferes with the loss of potassium through the cell membrane during muscular contraction and its return with relaxation may produce electrocardiographic changes. Experimental evidence for these concepts is incomplete at present. Levine, Merrill, and Somerville[26] suggested that the heart in potassium intoxication behaves as though a diffuse subendocardial injury had occurred. A similar type of response is elicited if the same surface is cooled. It is believed that the difference in concentration of potassium within and outside of the cell maintains its potential. Any type of injury may permit the migration of potassium to the cell surface, thus equalizing the potassium concentration on either side of the cell membrane. Thus, the electrocardiographic signs of myocardial injury may represent a local change in potassium concentration, probably in the subendocardial surface.

THE ELECTROCARDIOGRAM AS A GUIDE

Finally, in what conditions is the electrocardiogram most apt to be a reliable guide to the body content of potassium? This may be considered in four ways:

1. *Electrocardiographic Signs of Potassium Intoxication.*—If one bears in mind that the electrocardiogram reflects potassium concentration and not total potassium in the heart muscle, the electrocardiographic signs of potassium intoxication may be regarded as a highly accurate guide. In severe dehydration and acidosis, such as in diabetic acidosis or methyl alcohol intoxication, total potassium is very low, but total water content is even lower, thus producing a high potassium concentration in both blood and cell. Therefore, fluid must be given before the potassium deficit can be made up safely. It is possible, though not certain, that severe sodium deficit can imitate potassium intoxication in the electrocardiogram. Further work needs to be done here. At times, a myocardial infarction may mimic potassium intoxication in the electrocardiogram. In most cases, however, the electrocardiographic changes may be regarded as indicative of a dangerous level of potassium concentration in the body.

2. *High Blood Potassium Level as Reflected by the Electrocardiogram.*—As previously stated, electrocardiographic changes occur in 80 per cent of patients with blood levels above 6.8 meq. per liter and in even more of those with blood levels above 7.8 meq. per liter. This does not mean that the high blood level produces the electrocardiographic alterations.

3. *Electrocardiographic Signs of Potassium Deficit.*—These signs of potassium deficit may be imitated by numerous other conditions, such as beriberi, myocardial disease, and acid-base imbalance.[30] The changes in acid-base balance are

independent of the blood levels of sodium and potassium. However, in conjunction with a clinical story of potassium loss, they are very helpful. As a matter of fact, in some cases they accurately represent a body potassium deficit when the blood level may be misleadingly normal or even high.

4. *Low Blood Level of Potassium.*—A low blood level of potassium is a fairly accurate indication that body stores of potassium are low. Of course, the body content may be low with a normal or high blood potassium. In about 20 per cent of cases the electrocardiogram may be normal or, rarely, even show signs of potassium intoxication when the blood potassium is low. This seems to be most frequently true in the presence of severe renal disease. The reason for this is not clear unless it is because of the bizarre changes in the relative concentrations of other electrolytes plus the abnormal water distribution. Response of the low T waves and prolonged Q-T to potassium administration does not prove a potassium deficiency since abnormalities due to other causes may be normalized by giving potassium.[18]

SUMMARY

1. Magnesium excess and deficit produce no clearly defined change in the electrocardiogram which is of value clinically.

2. Calcium excess exhibits no reliable electrocardiographic aberrations. Calcium deficiency produces an anomaly which may be useful in conjunction with a clinical suspicion but which is duplicated by many other conditions. The prolonged Q-T interval due to increased S-T duration with a normal T width is to be distinguished from the prolonged Q-T interval due to a widened T wave associated with potassium deficiency.

3. Potassium intoxication is quite reliably represented by the electrocardiogram at blood levels above 7 meq. per liter and fairly so at 6.5 meq. per liter if a base line electrocardiogram has been taken to determine increase in the height of the T waves. The electrocardiogram indicates potassium concentration and does not show total potassium content which may actually be low.

4. Potassium deficit with a blood level below 3.0 meq. per liter is accurately depicted by the electrocardiogram in about 80 per cent of cases. The picture is far from specific, and clinical data are of great importance in interpreting the electrocardiographic abnormalities. At times, the electrocardiogram represents the body deficit more accurately than the blood potassium does, especially in renal disease. However, in some cases, levels as low as 0.9 meq. per liter have been reported with normal electrocardiographic findings.

5. The electrocardiographic signs of hyperpotassemia may be normalized in animals by injections of hypertonic sodium chloride without lowering the serum potassium concentration.

6. Some of the possibilities as to the cause of the electrocardiographic alterations are presented.

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VOL. 43 MAY, 1952 No. 5

Original Communications

PERICARDITIS

CLINICAL AND LABORATORY DATA OF 130 CASES

GEORGE R. HERRMANN, M.D., ERNESTO J. MARCHAND, M.D., GEORGEANNA H. GREER, M.D., AND MILTON R. HEJTMANCIK, M.D.

GALVESTON, TEXAS

PERICARDITIS is one of the most commonly overlooked clinical conditions. The manifestations of both acute and chronic involvement of the pericardium may be primary or secondary. It behooves us, therefore, to review and analyze our case material from time to time. We must be alert to the signs and symptoms and diagnostic laboratory studies that will make for greater accuracy and fewer failures in the diagnosis of this lesion. This is especially desirable now that antibacterial and hormonal agents are offering more in the way of curative therapy and earlier and safer preparation for radical surgical treatment. Pericarditis for many years has been the subject of interest in our clinic and our cardiovascular research laboratories.[1]

Pericarditis is a somewhat uncommon clinical condition, yet it warrants reconsideration at this time. Griffith and Wallace[2] recently analyzed 1,000 post-mortem cases autopsied over a period of ten years, which showed evidences of pericarditis. They pointed out that pericarditis was found in 5.8 per cent of their autopsy series; this was twice the incidence in clinical practice. Furthermore, there were noted changes in the incidence of certain etiological types as compared with the data reported twenty years ago by Smith and Willius[3] and that reported fifty years ago by Preble.[2]

In recent years bacterial pericarditis, including the tuberculous type, has decreased, while pericarditis secondary to cardiovascular disease, uremia, and malignancy has increased with the increase in the life span of the population. Carmichael, Sprague, Wyman, and Bland[4] have restudied their fifty acute, nonspecific, or virus pericarditis cases and emphasized the apparent increase in the condition, the characteristic clinical picture, and the excellent long-term prognosis.

From the Cardiovascular Service of the University of Texas Hospitals, Galveston, Texas.

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